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VOLUME X NUMBER 4

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STUDIES FROM THE Department of MEDICINE

1918/21

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477 FIRST AVENUE
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CONTENTS

Being Reprints of Studies Issued from the Department of Medicine

1918-1921

1. Notes on the Diagnosis of Bronchopneumonia and Its Complications. **Nellis B. Foster**
(From the American Journal of the Medical Sciences, January, 1921, CLXI, 1)

2. A Consideration of the Surgical Hazards in Diabetic Patients. **Nellis B. Foster**
(From Annals of Surgery, March, 1920, LXXI, 382)

3. Arteriosclerosis: The Three-fold Menace of the Present Day. **Charles E. Nammack**
(From Medical Record, November, 1920, XCVIII, 757)

4. Clinical Calorimetry. XXIX. The Metabolism in Tuberculosis. **William S. McCann and David P. Barr**
(From the Archives of Internal Medicine, December, 1920, XXVI, 663)

5. Studies of the Respiratory Mechanism in Cardiac Dyspnea:
I. The Low Alveolar Carbon Dioxide of Cardiac Dyspnea.
II. A Note on the Effective Lung Volume in Cardiac Dyspnea.
III. The Effective Ventilation in Cardiac Dyspnea.
David P. Barr and John P. Peters, Jr.
(From the American Journal of Physiology, December, 1920, LIV, 307-354)

6. The Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of the Blood of Normal Resting Invalids.
John P. Peters, Jr., David P. Barr and Francis D. Rule
(From the Journal of Biological Chemistry, February, 1921, XLV, 489)

7. The Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of the Blood in Cardiac Dyspnea.
John P. Peters, Jr. and David P. Barr
(From the Journal of Biological Chemistry, February, 1921, XLV, 537)

8. The Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of the Blood in Severe Anemia.
David P. Barr and John P. Peters, Jr.
(From the Journal of Biological Chemistry, February, 1921, XLV, 571)

9. The Significance of Yellow Spinal Fluid. **Charles H. Nammack**
(From the American Journal of the Medical Sciences, April, 1920, CLIX, 540)

10. A Case of Von Jaksch's Anemia Occurring in a Child 5½ Months Old. **William C. Thro**
(From Proceedings of the New York Pathological Society, January-May, 1919, XIX, 6)

11. Some Unusual Blood Cells in Diseases of Bone Marrow Origin. **William C. Thro**
(From the Journal of Medical Research, July, 1918, XXXVIII, 385)

12. Bacteriologic Studies in Chronic Arthritis and Chorea. **John H. Richards**
(From the Journal of Bacteriology, September, 1920, V, 511)

Extracted from the American Journal of the Medical Sciences
January, 1921, No. 1, vol. clxi, p. 1.

NOTES ON THE DIAGNOSIS OF BRONCHOPNEUMONIA AND ITS COMPLICATIONS.

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Reference to any standard text will lead to the inference that primary bronchopneumonia in adults is not a common disease. That it is the usual type of pneumonia in children is accepted as well as that "terminal pneumonias" are commonly of the catarrhal variety. But that bronchopneumonia is at all confined to the extremes of life, childhood and old age is, I believe, incorrect. It will be the purpose of this paper to present evidence indicating the frequency of this type of pneumonia, to discuss the several pathologic and clinical pictures that may be grouped under the generic heading of broncho- or lobular pneumonia and their more serious complications.

In assuming a position which may seem at variance with usual conceptions of incidence, an explanation is appropriate as to why bronchopneumonia may at times escape detection and be passed over as simple bronchitis. The explanation is simple: (1) the physical signs are frequently transitory, and (2) the patient may not seem sick—that is, sick enough to excite careful examination. Pneumonia is closely associated in our mind with a group of rather definite symptoms and, in the absence of these, the examination made is liable to be either perfunctory or entirely omitted. The fleeting, evanescent character of the physical signs can hardly be appreciated unless one has experience in ward-teaching. Time and again the signs found at morning rounds were gone in the area marked when the patient was shown at the afternoon clinic, and this explains the development of hospital routine regarding radiograms. The instructor was at times in sore need of demonstrable evidence. From this the logical step was natural of radiographing many cases of "simple bronchitis" in which no sign of consolidation had at the time been noted. The results of these examinations were illuminating; at first in revealing what we did not detect and later in confirming a suspected lesion. What interpretation is to be placed upon a record of this sort? A healthy man of twenty-six years was admitted

to hospital January 20 complaining of a cold which he attributed to a wetting two days before. He had felt a little feverish the night before admission, but not sick. He said he did not feel sick enough to be in bed, but a "bit fagged." His temperature was 101°, respiration 22, pulse 90. Examination showed only rales scattered throughout both lungs: No dulness; no change in breath sounds; pectoriloquy absent. A radiogram taken on the day of admission showed an area of density, the size of an egg, just above the heart shadow in the left chest an inch from the hilus of the lung. On January 22 the shadow was still present: the patient had improved and the fever had gone. A final plate, taken on January 28, showed only a slight residual clouding in the area mentioned. At no time had there been physical signs other than those of a bronchitis (rales): at no time had the patient seemed or felt really ill. A repetition of this experience over and over gave ground for the hospital dictum—"bronchitis is rarer than a bronchopneumonia"—and this apparently extravagant assertion accords with my experience in private practice. That the patient may not feel sick, nor look more so than one does with a cold, that the temperature is but slightly elevated is sufficient explanation for neglect of searching examination. History records the "incidence of most diseases has increased with their recognition."

Not only is bronchopneumonia a very common disease in hospital practice, but the incidence will be found high among healthy young men in colleges, as I have had opportunity to observe, and it was one of the common diseases in the cantonments at periods when no epidemic prevailed. Furthermore the nature of disorders which are traced back to "colds" would be best explained by pneumonia, and these disorders are not few.

Bronchopneumonia, as the name indicates, is very often purely an extension of an infection from the smaller bronchi to contiguous pulmonary tissue. The disease seems to have been first described by Bartels, although Laennec mentioned the scattered areas of infiltration found in some cases of catarrhal bronchitis. Common usage has made the terms bronchopneumonia and lobular pneumonia synonymous. Some pathologists, however, draw distinctions which are not generally accepted, and until the processes are better understood in their mode of production, are useless. The morphology of broncho- or lobular pneumonia is determined largely by the type of infection, and, to some extent at least, by whether the infection enters through the respiratory tract or the blood stream. The more general aspects which characterize the pathology of lobular pneumonia have a common basis in all types. On section of the diseased lung the fresh surface has a notably "patchy" character; certain areas are raised, and at the center of these areas may usually be found the bronchi, seen as grayish spots from which pus may be expressed. The involved areas may be numerous and

discrete, or they may coalesce into large consolidations; even when a considerable portion of a lobe is involved in the consolidation the picture does not often resemble lobar pneumonia. The cut surface is less granular and there is not liable to be much fibrin or leukocytic detritus as with lobar pneumonia. Between the areas of consolidation atelectasis occurs, due to stoppage of the bronchioles, with resorption of air and resulting collapse of the alveoli. In its earliest stage scattered areas of bronchopneumonia may appear as numerous discrete, minute tubercles, shotty to feel, gray or brownish in color, and surrounded by areas of reddish atelectatic tissue. When the lung presents this picture at necropsy it may be mistaken for miliary tuberculosis (and the radiogram is equally misleading). A later stage represents the enlargement of these small areas with coalescence. Thus a whole lobe may be involved, but the patchy character of the cut surface is usually preserved: massive, confluent, lobular pneumonia. Minor differences are determined, it seems, by the nature of infection and the resistance of the individual. The salient fact in this pathologic process is that it takes origin in a bronchiole. Following a bronchus into a diseased portion of the lung by dissection discloses that the consolidation is terminal or lateral to a bronchus.

Bronchopneumonia is usually thought of as a complication of typhoid fever ("typhoid pneumonia"), measles, diphtheria and occasionally of scarlet fever. The causative infecting agents are numerous. With the primary type of bronchopneumonia the pneumococcus is often found, even Type I pneumococci has been repeatedly isolated from sputum of some of my cases. Pneumococcus type IV is more common, while probably a majority of the cases of lobular pneumonia are due to streptococci, either as a primary infection or mixed with some other organism. The role of the streptococcus in these processes is by no means clear, in spite of the fact that it has been repeatedly isolated from both the sputum and from the lung tissues of cases dead of pneumonia. The reason for some doubt rests in the conception that the streptococcus infections are prone to be secondary. Weichselbaum illustrated the point years ago with reference to empyema, which may, in the initial stage, show only pneumococci in the pus; later the pneumococci are overgrown and disappear and the pus contains only streptococci.[1] For example, measles pneumonia, a typical secondary infection, is predominantly a streptococcus pneumonia. The primary invader may be an organism of relatively slight virulence, but, given a predisposition, the tissues are made vulnerable by this trivial infection and the streptococcus finds a suitable environment for growth.

[1] The advent of filtrable viruses further complicates the question and postpones definite decision. In relation to this question, see the communication of Roux to the Académie des Sciences, at the November meeting, 1918, dealing with pathogeneses of influenza.

Coryza is often due apparently to an invasion of the Micrococcus catarrhalis, an organism of weak pathogenicity, a secondary infection with streptococcus takes place and pneumonia develops. This expresses the present conception of the mode of origin of a group of diseases due to streptococcus infections, and it is the sole scientific basis for the face mask so much used in military hospitals; protecting an individual susceptible on account of some slight infection from inhaling streptococci thrown out by persons already infected. The practical difficulty in this prophylaxis is that so many healthy persons harbor Streptococcus hemolyticus in the throat. Mathers found hemolytic streptococci in the throats of 70 per cent. of a healthy organization at Camp Meade. These questions have not only scientific interest, but are in the front rank of practical considerations when diseases such as measles are to be cared for. For some time pediatrists have recognized that the incidence of pneumonia complicating measles is higher in even very good hospitals than among children cared for in their homes, and an impression growing toward conviction is notable that, under certain conditions, pneumonia may spread as a contagion in measles wards. The factor that is outstanding in my experience in determining the incidence of pneumonia complicating measles is the season of the year; in the cold months there has been a higher percentage of pneumonia than occurred in the warm parts of the year, and this has been true even with the most rigid methods of individual isolation. Is the body's resistance so generally lowered by cold weather?

The factors which predispose to pneumonia may be classed under two headings: those which lower the vitality of the individual and those which lower the resistance of the pulmonary tissues. Under the first heading would come not only the diseases generally recognized as terminating with bronchopneumonia, chronic and cachectic diseases and certain acute infections, such as the exanthemata, but also those conditions which suddenly reduce immunity, and here fatigue takes first place. With sound, healthy individuals no factor seems to be so potent in lowering resistance to infection as is fatigue. Probably this is in some degree true of all infections; it can hardly be controverted in relation to pneumonia. Other factors of significance are hunger and chilling from exposure. All of these factors more or less enter into consideration with all types of pneumonia, lobar as well as lobular. In one case the invasion is prompt and sudden and lobar pneumonia develops; in another, more insidious or perhaps in the beginning milder, a "simple cold" with bronchopneumonia later.

Of the factors which lower the resistance of pulmonary tissues mild and even trivial infections are paramount: trivial infections are ignored. It was notable in all cantonments that those organizations that sent their cases of minor sickness to hospital had the lowest incidence of pneumonia. The significance is clear: with a

mild bronchitis a bed is the best prophylactic against pneumonia. The resistance of pulmonary tissues to infection is also lowered by mechanical and chemical irritation; dust, especially sand, gases and smoke, ether and chloroform. Postoperative pneumonia is due evidently to several factors: the technical skill of the operator, the purity of the ether and skill of administration and the care of the patient during the period while he is recovering from the anesthetic, especially respecting warmth. In several clinics, where opportunity has come to me to study many cases of pneumonia following operation, I have not been able to trace the cause nearer than outlined above. The question is important and deserves more careful study than has been given to it.

In *resume,* it may be briefly stated that any circumstance which lowers the vitality of the organism as a whole, or by irritation injures the pulmonary tissues, locally, predisposes to pneumonia. The invader is always at hand and the invasion depends upon the host.

Symptoms. The clinical picture of bronchopneumonia is most variable. At one extreme is the case with signs and no symptoms other than fever, at the other extreme is a clinical picture of the severest form of pneumonia. In truth, there are cases with marked symptoms and no corresponding signs, and others with slight symptoms and clearly defined signs. The mild cases offer some difficulty in diagnosis and are often overlooked, although deserving attention on account of the frequent sequelæ. It so often happens that the patient seeks help only on account of an annoying cough. With scarcely any pyrexia the tendency is natural to dismiss the case as one of acute bronchitis requiring no thorough examination of the lungs. Allowed up and about, perhaps at work, the patient's condition becomes serious before its nature is recognized. I have known this to occur not infrequently. The patient then takes to his bed only when exhausted or in collapse. With pneumonia little enough can be done for the patient other than securing him rest and protection of his vitality, and this should not be delayed.

Occasionally the period of active infection is passed before the patient consults a physician. A number of cases belonging in this category have been encountered where relief was sought from a persistent cough following a "hard cold," and examination disclosed an area of consolidation, but no fever or other sign or symptom. Delayed resolution of this sort may be, and often is, mistaken for a tuberculous consolidation. A young physician consulted me for a confirmation of the diagnosis of pulmonary tuberculosis made by a specialist. The patient had had a severe bronchitis some two weeks before but had kept at work in spite of fever. The physical signs were confined to an area in the upper portion of the left lower lobe —a consolidation a couple of inches in diameter. This spot slowly resolved in the course of a month. With vigorous, sthenic indi-

viduals, bronchopneumonia is, I am convinced, occasionally experienced as a "bronchial cold," and with no more results.

The onset is occasionally sudden, resembling in this respect lobar pneumonia; more often there is a gradual development, commencing as a "cold," with slight cough, becoming more severe until the patient is driven to his bed. Pleural involvement occurs late in contrast to lobar pneumonia. In the early period of the disease the temperature may not be above 101° F., the pulse but slightly increased and the respirations not accelerated. Drenching sweats are common; cough is annoying and exhausting. The sputum varies; there may be considerable amounts of mucopurulent material, with no obvious admixture of blood—with other cases the sputum is greenish pus, or, again, it resembles brick dust in color. When the infection is severe, dyspnea is often a striking symptom, and this, with the marked cyanosis, recalls the old name of the disease "suffocative catarrh." With many cases death appears to result from asphyxia rather than from a wearing out of the myocardium, as in lobar pneumonia.

The nervous symptoms are most striking. Delirium is common, not of the low, muttering type, but violent, often maniacal. A peculiar typhoid state with delirium, marked tremor and coma vigil is occasionally noted. Many patients complain of excruciating headache, and with this signs of meningismus are frequent. Relief is often prompt, following lumbar puncture and the removal of a half ounce of fluid. Headache with a stiff neck and a suggestive Kernig sign is an indication for lumbar puncture. The fluid in these conditions is under considerably increased pressure—the first half-ounce running so fast the drops cannot be counted. I have gained the impression that with some of these cases not only does the headache abate, but respiration is improved by relieving the intracranial pressure.

With severe bronchopneumonia the picture at times presented by the patient when the disease is at its height differs in many respects from lobar pneumonia. The deep, livid cyanosis arrests attention. The picture of suffocation with an excited, alert mental state; the sweating; cold, clammy extremities in spite of a strong, regular pulse—a clinical picture not readily overlooked.

A type of pneumonia called interstitial is seldom recognized clinically, except by inference. The early symptoms suggest the onset of lobar pneumonia. Examination of the patient discloses signs of fluid in the pleural cavity. These are the cases of primary empyema (so called). The characteristic feature is the rapid formation of the pus. A patient having only symptoms of an infection may, within six or eight hours, develop symptoms of intrathoracic pressure, with signs indicating a pleural cavity full of fluid. To one who has not watched such cases and seen the pus return after aspiration and fill a cavity overnight the peculiar feature of this infec-

tion is scarcely creditable. Interstitial pneumonia received some attention in cantonment hospitals during last winter. Kaufmann's[2] classical description covers the essential features of the pathology.

Diagnosis. The diagnosis of bronchopneumonia cannot invariable be arrived at from the physical signs alone. Those somewhat unusual cases of multiple, discrete foci give none of the typical signs of consolidation, and these could not be expected when the foci are no larger than peas. The picture presented by the radiogram is misleading to the unwary and is not infrequently regarded as miliary tuberculosis, which, indeed, it may resemble post mortem. The signs in these cases are those we customarily associate with bronchitis. There is, however, something more than rales to be heard; a variability in the intensity of the breath sounds in contiguous areas is peculiar and arrests attention if one be on the lookout for this phenomenon. However, in some cases the diagnosis must be inferred, the temperature being too persistent and an increased respiratory rate speaking against bronchitis. When possible to procure one, stereoscopic radiograms may aid in confirming the diagnosis.

Even relatively small areas of consolidation are detectable by a skilled technic. Unless the area involved be near the costal pleura, however, impairment of resonance and frank change in breath sounds will not be notable. The change in the character of the signs over suspected spots at different examinations is in itself significant. The fleeting and migratory character of the consolidations in lobular pneumonia is peculiar to the disease. The earliest definite sign, and the one of most help when other signs are equivocal, is the change in the whispered voice which is transmitted to the ear with an abnormal clearness and with a slight nasal quality. Transmission of the whispered voice is a helpful sign in the recognition of changes of density in the lung substance and is often the earliest sign in all types of pneumonia. Because this sign is so frequently neglected some amplification is appropriate. A confusion exists in the minds of many concerning the significance of variations in the transmission of sound vibrations, because the attention is given only to intensity or loudness of sound, whereas variations in quality of the sound or in its pitch are even more significant and the examiner must take pains to keep these several features entirely distinct. For example, sounds of low pitch are better transmitted to the chest wall through normal lung than are equally intense sounds of higher pitch. With a solid lung, on the other hand, vibrations of all pitch are equally well transmitted. In bronchopneumonia small areas of consolidated lung substance are surrounded by air-containing lung, and this latter appears to "dampen" some vibrations more than others; the overtones being least affected are transmitted to the chest wall.

[2] Speziellen Path. Anat., 1911, 261.

Another factor is the bone conduction of the spoken voice which enters as a confusing element in auscultation; this confusion is less pronounced or negligible in whispered pectoriloquy. Flint called attention to elevation of pitch as a sign of consolidation and the nonessential factor of mere intensity of sound.[3] It has repeatedly happened that whispered pectoriloquy was the only definite physical sign over small areas where consolidation was demonstrated by radiogram. Where the consolidation is of considerable size there is usually no difficulty in its recognition.

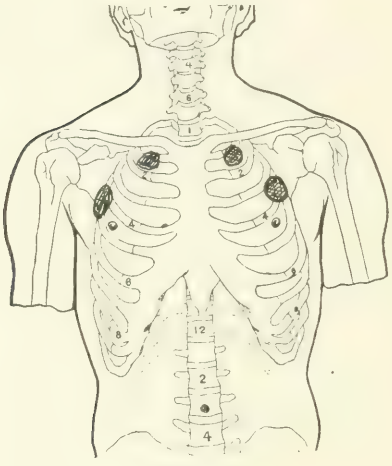

FIG. 1

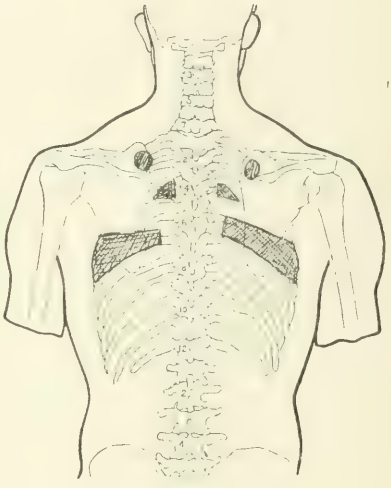

FIG. 2

Bronchopneumonia, alike with lobar pneumonia, shows a predilection for the lower lobes and is noted most frequently in certain areas which are illustrated in the charts (Figs. 1 and 2). The mild cases, infections of low virulence, may not come under observation until convalescence, and then the question of tuberculous infection is often uppermost. The site of the consolidation is of help in decision on this question, as tuberculous infections are not usually located in the bases of the lungs. The confusion of tuberculosis with delayed resolution of bronchopneumonia has been the subject of frequent remark by those especially interested in tuberculosis,[4] and it will be recalled that the mistake was made so often in the army that it became necessary to restrict the diagnosis of tuberculosis to those cases with tubercle bacilli in the sputum. Comment on this significant fact is hardly necessary.

[3] See a clarifying analysis of these factors by Adams and Montgomery, Jour. Am. Med. Assn., 1919, lxxii, 987.

[4] Ash: Jour. Am. Med. Assn., January 2, 1915, lxiv, 11. McCrae and Funk, idem, July 19, 1919, lxxiii, 3.

Complications in lobular pneumonia, according to my case records, are more common than with lobar pneumonia. Except in young children, otitis media can hardly be overlooked, but empyema and pulmonary abscess very frequently escape recognition. Some experience outside of medical centers has convinced me that the so-called "septic pneumonia" of rural districts is usually empyema. Two erroneous notions are primarily responsible for the failures of recognition of empyema: (1) the idea that empyema is accompanied by a definite type of temperature curve, and (2) the idea that empyema gives rise to definite, characteristic physical signs. Both of these conceptions are narrow and misleading. The diurnal variation of temperature which is expected is so frequently absent that the type of fever is of little aid in diagnosis. While it may be true that with empyema following lobar pneumonia the temperature comes to normal in the majority of cases and then again becomes elevated, this fact is seldom applicable to the fever of empyema following lobular pneumonia. The accompanying charts (1 and 2) illustrate the diversity of febrile reactions. In some cases a sharp rise in the pulse-rate is more significant than the temperature curve.

Occasionally small pleural abscesses become so walled off that there is slight or no fever, the patient remaining an invalid for indefinite periods. In one case of this type the history pointed to an ambulatory pneumonia fourteen months before as the cause of the abscess.

The physical signs of empyema are so variable and departures from the text-book descriptions so frequent that it is necessary to hold broad and elastic conceptions and abandon the definite picture customarily held. Some cases undoubtedly show characteristic changes on examination, such as a dull or flat percussion note, impaired or absent vocal fremitus, with distant suppressed breath sounds approaching a bronchial type; but again it must be recognized that exceptions are exceedingly common.

Pleural abscesses tend to be sacculated and the surrounding lung tissue may be either consolidated in part or markedly emphysematous. The variations in these structural changes in the lung parenchyma give origin to variations in physical signs; moreover, there seems to be a tendency for the focus of suppuration to take place first in a fissure between the lobes, with subsequent extension. When firm adhesions have been formed between the costal and parietal pleura there may be a thin lappet of air-containing lung between the ribs and pus. Postmortem examinations have revealed conditions of this sort and helped in an understanding of the marked variation in the peculiar physical signs. The fact should be emphasized that in many cases it is absolutely impossible to determine, by physical signs alone, whether the diseased condition in the lung is consolidation, fluid or both. The diagnosis, under these circumstances, can be determined only by exploratory puncture. Modified

skodaic resonance in areas of the lung adjacent to collections of liquid has been to me of great assistance in diagnosis. The note elicited by percussion in the upper axillæ or over the lower portion

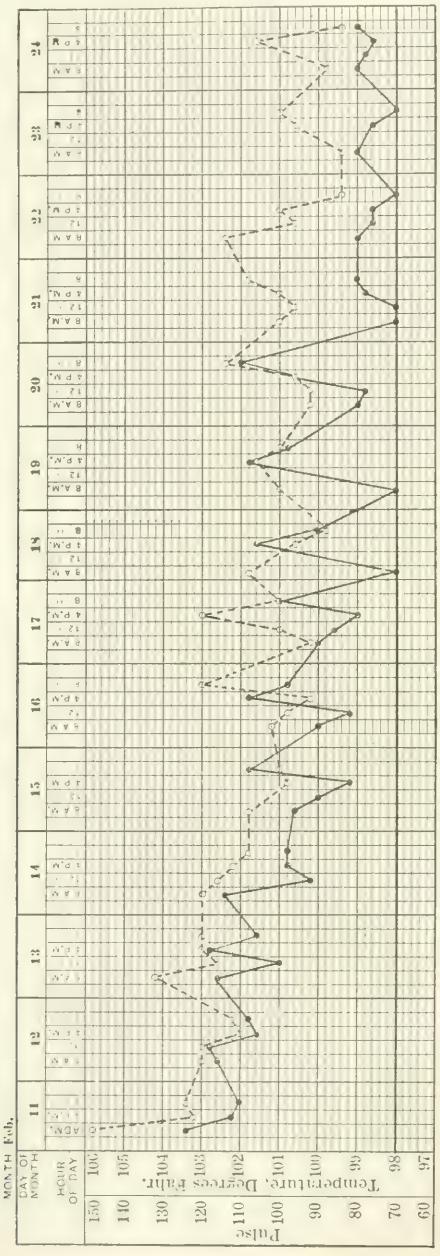

CHART I.—Typical bronchopneumonia. Empyema demonstrated on 19th.

of the upper lobe overlying or adjacent to fluid has a high-pitched tympanitic quality approaching the amphoric. This peculiar alteration in the percussion note I have only seldom detected in a like degree over areas of lung adjacent to consolidation. This skodaic resonance is so marked that in several instances examiners of skill have mistaken the underlying condition for cavity. To me this sign is more significant than impairment of resonance or even flatness in the percussion note over fluid. Fluid is not always detected, even when present, because the exploring needle is not introduced in the proper area and sometimes, indeed, the fluid cannot be found. An interesting example of this occurred in my service at Camp Meade Base Hospital. A patient developed, following pneumonia, typical

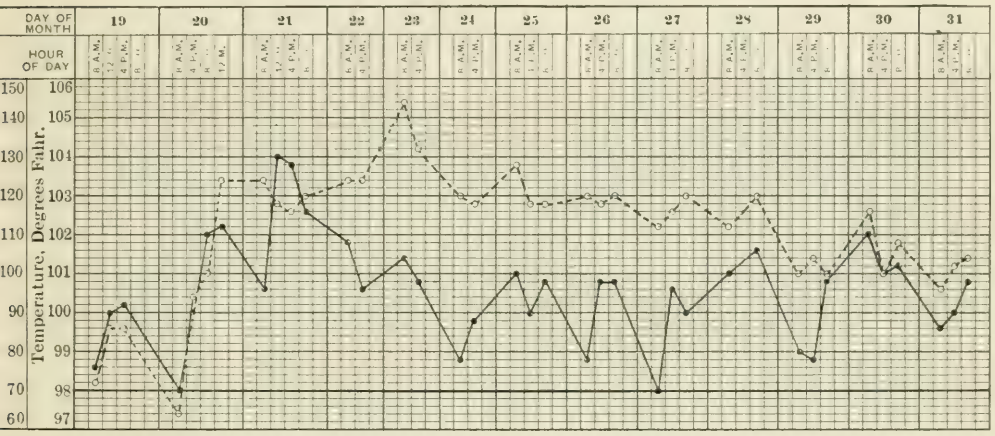

CHART II.—F. W., aged twenty-eight years. Case of Dr. Payne. Interstitial pneumonia (?). Empyema. On 20th, signs of slight bronchitis only; pain in the left chest. On 21st, at 10.30 A.M., careful examination failed to disclose suspected pneumonia; at 3.30 P.M. of same day, dulness, impaired fremitus and distant vesicular breath sounds over the left base posteriorly, Exploratory puncture. Pus. Infection due to Streptococcus hemolytic. Aspirations; operation on 30th.

signs of fluid in the pleural cavity. There was no dissent concerning the diagnosis. The chest was needled by the ward surgeon with no success, by the assistant chiefs, the chief, and later by others on the staff. No interspace from spine to sternum in the suspected area escaped. The patient finally improved, the fever disappeared but the signs persisted. One day while sitting on the ward porch he had an attack of severe coughing and began to bring up pus. Some was lost, but the nurse saved over a pint as evidence of the correctness of the diagnosis. The patient made a perfect recovery. I know of no guide that is infallible; certainly physical signs are often enough misleading. In many cases, however, there can be detected, by careful examination, some spot where pressure produces acute pain, and I have found that this area of hyperesthesia is the most

promising site for exploration. The accompanying illustrations (Figs. 3, 4, 5 and 6) are of some interest, not only in depicting the peculiarity of physical signs in some cases of empyema but also in

FIG. 3.—Atypical signs in empyema. Anterior view: Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T.*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S.*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

showing that several unsuccessful explorations do not prove the absence of fluid. There is no explanation for the fact that the area

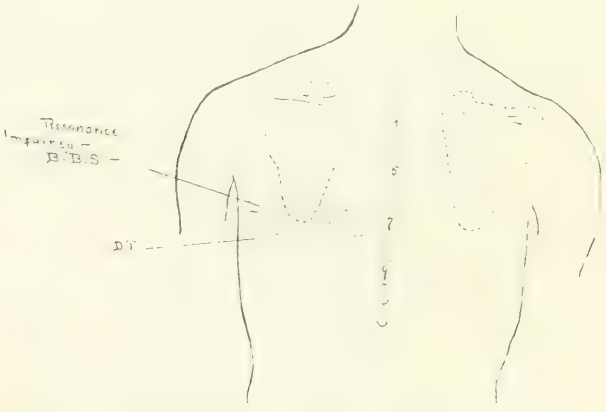

FIG. 4.—Atypical signs in empyema. Posterior view of same case as shown in Fig. 3: Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T.*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S.*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

of maximum flatness is needled so often with no result, and a proximate hyperresonant area is shown by puncture to overlie fluid. It must also be borne in mind that there may be more than one separate collection of pus.

Finally, in the diagnosis of empyema I cannot too strongly disagree with the teaching that there is always a displacement of neighboring viscera, *i. e.*, heart or liver. Abscesses in the pleura of con-

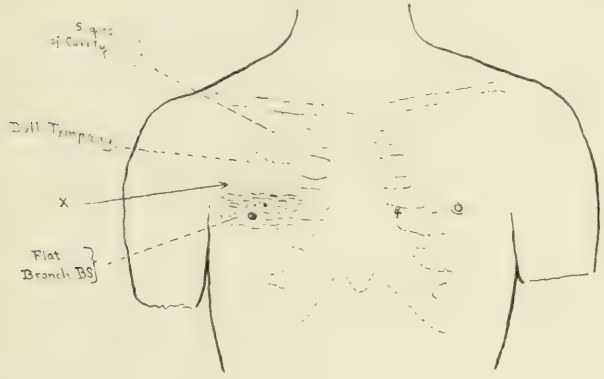

FIG. 5.—Atypical signs in empyema. Anterior view; Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

siderable size can develop in a lung bound down by adhesions without appreciable displacement of neighboring organs. On the other

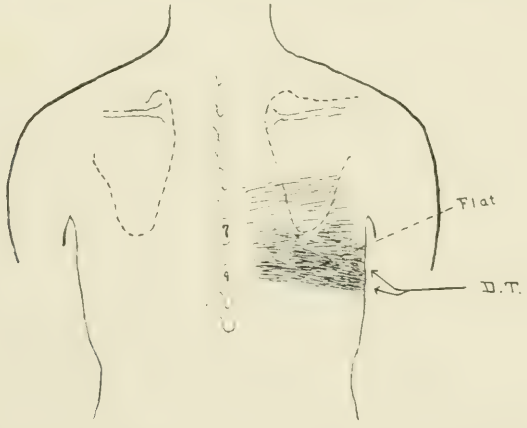

FIG. 6.—Atypical signs in empyema. Posterior view of same patient as shown in Fig. 5: Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

hand, marked emphysema in the uninvolved lung may produce displacement of the heart toward the diseased side. This fact has been noted at autopsy.

In the treatment of these cases of empyema the conception no longer holds that diagnosis should be followed by immediate thoracotomy. Early operation, before firm adhesions have been formed surrounding the suppuration, leads to pneumothorax and infection of the whole pleural cavity. The mortality under these circumstances is known to be high. Repeated aspirations, on the other hand, allow time for adhesions to form; the patient during this interval recovers to some extent from the severity of the infection, and, when finally subjected to operation, not only is the local condition in the lung walled off and better suited for drainage, but the patient's general resistance is higher and he is better able to withstand the shock of operation. A small percentage (in my experience about six) of the cases of empyema will recover following repeated aspiration alone and never require surgery.

The question arises at this juncture, For how long a period should aspirations be continued: in other words, for how long can operation be postponed? The answer is not as difficult as it might seem. So long as the patient continues to improve operation can be deferred. The criteria for improvement are better appetite and sleep, a lower fever and pulse-rate and evidences of diminished infection, such as less sweating and improvement in the patient's sense of well-being and strength. On the average this period of improvement will continue for about ten days. With a few the period is prolonged into convalescence. In some cases the reason for final operation is that the pus becomes so thick that drainage cannot be effected through a large needle. With others the indication for operation is an increase in the temperature, a failing appetite and the general appearance of the patient.

Of the relation of pulmonary abscess to bronchopneumonia we have but little knowledge. In three of my cases of abscess of the lung the history indicated very strongly a beginning of the affection in bronchial pneumonia. In one of these cases this is more than probable, since the pneumonia developed after operation, the so-called ether pneumonia. The reason for mentioning pulmonary abscess in the present connection is that occasionally pulmonary abscess can be cured by artificial pneumothorax. This procedure is indicated, however, only when there are no pleural adhesions, since, of course, with such adhesions the desired collapse of the lung cannot be produced. In two cases, where the abscess was in the mesial portion of one of the lower lobes, artificial pneumothorax resulted in an abatement of the symptoms and the last case treated is well up to the present time, a period of about two years since treatment was discontinued. When the abscess is near the pleura, as unfortunately it frequently is, adhesions usually occur and the only cure under these circumstances is lobectomy.

The most common of the sequelæ of bronchopneumonia, alike with lobar pneumonia, relates to the heart. Slight involvement of

the myocardium, as manifested by breathlessness on exertion, is so common, following all types of pneumonia, that it is to be regarded as one of the incidents of convalescence. With not a few individuals, however, this symptom is prolonged for a number of months. Affections such as described are by no means confined to the elderly or to those who have some preëxistent cardiac disorder, but are manifested not infrequently in robust young men. The physical signs are seldom clear cut, and of themselves would hardly disclose the nature of the disorder. The heart sounds may not be as clear as they should be and occasionally a systolic murmur can be heard at the apex. But these signs can be noted in a considerable number of apparently healthy persons. The significant fact is the symptoms of circulatory embarrassment coming on after an acute infection. From a therapeutic point of view it is important first to recognize the nature of the disorder, with a view to protecting the patient against premature severe physical exertion. Time alone corrects the great majority of these disabilities. In addition, well-supervised graduated exercises have a distinct use, as was demonstrated on such a large scale in the military convalescent camps.

In conclusion, it is desirable to emphasize that bronchopneumonia is a common affection in young, robust individuals, and that, on account of the physical signs, the disease may, in mild cases, be easily overlooked. The treacherous character of bronchopneumonia and the seriousness of its complications and sequelæ indicate the importance of early recognition and adequate protective care.

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A CONSIDERATION OF THE SURGICAL HAZARDS IN DIABETIC PATIENTS

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An increased risk of operation when the surgical disease is complicated by diabetes is quite generally recognized, but it is not so commonly appreciated that complications which might be regarded as surgical are the immediate cause of death in a large proportion of cases of diabetes. While statistics based upon hospital records are not completely satisfactory, since only certain types of disease are apt to be admitted to hospital, yet, in a general way, data of this sort are significant. A careful review of the clinical records of two good hospitals brought out the following somewhat surprising facts. Of the fatal cases of diabetes dying beyond the third decade of life, about 60 per cent. of the fatalities occur following operations. Of the surgical cases with a fatal termination, 70 per cent. die in coma. It has been the habit, apparently, to endeavor to make some estimate, in cases such as the above, as to the degree of severity of the diabetic state, and the terms commonly employed are mild, moderate, and severe. The estimations of the severity of the disorder were based evidently upon the glycosuria. Accepting this classification for what it is worth, it is found that coma occurs after operation as often in mild cases of diabetes as in the apparently severe, which, of course, means that the estimations were made upon faulty criteria.

Surgeons are accustomed to classify operations as minor or major, into which classification a number of factors enter, but the meaning of these terms is quite generally understood. Using these terms in the sense commonly accepted we find that the mortality in diabetic patients is higher following minor operations than it is in general for major operations. Of course, one recognizes here at once that major operations might not, as a rule, be attempted on diabetic patients, certainly not without consideration, but this brings more into contrast the erroneous estimation often placed upon the hazard of minor surgical procedures in diabetic patients.

These preliminary considerations bring up the questions which I wish to discuss. Although surgeons and internists alike recognize that an

increased hazard attaches to any surgical operation when this operation is done upon a diabetic patient, yet it is not so generally recognized that the factors which go to make up the increased risk can be analyzed and to a very high degree estimated.

From what has already been said it would seem evident that glycosuria is not a reliable guide in the estimation of the severity of diabetes, in fact, it is doubtful if it is any guide at all further than a rough diagnosis. Glycosuria does not invariably connote true diabetes mellitus; on the other hand, the absence of glycosuria does not completely exclude this disease. It is generally recognized at the present time that diagnosis and much more the estimation of the severity of the disease depends upon the degree of hyperglycæmia under varying conditions of diet.

It is not inappropriate in this connection to call attention to the type of diabetes which may not show glycosuria. Where the disease has existed for a considerable period of time renal degeneration quite commonly occurs. The earliest clinical manifestation of this complication is very often an increase in blood-pressure. In time it is noticed that the glycosuria gradually abates and, in not a few individuals, completely disappears; so that one is told by the patient that at a certain period in his life he suffered from diabetes for a number of years, but of this was "cured." A thorough examination, and especially blood-sugar estimations, reveals the true condition, which in effect is that the pathological condition in the kidney has progressed to a degree so that even a considerable increase in the blood sugar is not manifested by sugar in the urine. One may accept it, then, as established that diabetes mellitus can be diagnosed and the severity of the disease estimated only by determining the hyperglycæmia.

Relative to our discussion are those factors which influence the normal blood sugar by increasing it, since they produce the same effect to a greater extent in the diabetic state. Chief among these must be mentioned infections. Persons who are not afflicted with any metabolic disease show, when they are the subjects of chronic infections, disturbances in the metabolism of sugar, and this disturbance is characterized by an increase of the blood sugar beyond the normal limit after the ingestion of glucose and a prolongation of the blood-sugar curve beyond the normal two hours. Chronic infections in diabetic subjects induce a similar change, which is expressed clinically in the difficulty experienced in reducing by diet the hyperglycæmia to normal; moreover, this disturbance, produced by infection, implies on the part of the diabetic organism an increased difficulty in the metabolism of glucose and, on that account, the tendency to acidosis is more marked. These fundamental facts are well exemplified in even minor infections in diabetic individuals.

A diabetic patient may have progressed in a most satisfactory manner for a considerable period of time and he may have acquired an ability to utilize an appreciable amount of carbohydrate, the blood sugar remain-

ing during this period practically normal. At this juncture he develops tonsillitis. The blood sugar increases and, even though the patient may take scarcely any food, sugar returns to the urine. A decrease in the metabolism of glucose is manifested by some degree of acidosis, even after the infection has passed. It may require a considerable period of time before conditions are restored to what they were prior to the intercurrent infection. In children relatively mild infections of this sort not infrequently lead to fatal acidosis and coma. The same changes in the metabolism accompany the numerous infections which require surgical treatment, carbuncles, cellulitis. The next factor that is important, in cases where surgical treatment may be required, is the influence of anæsthesia upon the carbohydrate metabolism. Every surgeon knows that glycosuria is occasionally manifested after anæsthesia. Accompanying this disturbance there is more or less acidosis, depending upon the nature of the operation and the period of time of anæsthesia. Here, then, as with infections, we have a factor which aggravates and intensifies the peculiar disorder which characterizes diabetes. The third important factor which comes in for consideration is the predisposition of the diabetic to infections and the diminished recuperative power manifested by his tissues when infections are established.

In resumé of these detailed facts it would seem evident, then, that the severity of diabetes in any given case can be estimated only by blood analyses, that infections tend to increase the severity of the disturbance of carbohydrate metabolism and, in that way, bring about a variable degree of acidosis and that the low resistance of the tissues to infection prolongs and intensifies the carbohydrate disturbance and hence of the acidosis. Anæsthesia, and especially ether, intensify the disordered processes.

A recognition of these facts should make it possible, it would seem, to determine, at least, when operation cannot be borne by a diabetic subject. These facts also suggest that an estimation of the hazards is possible in border-line cases. The chief danger is always acidosis and coma, and, for that reason, a determination of this factor is the prime requisite. Estimations of the CO_2 combining power of the blood give a very definite idea of the degree of acidosis, and this estimation requires only a few minutes. Normal blood shows a combining power for CO_2 above 55 per cent. Severe degrees of acidosis are evidenced by a combined power of 20 per cent. or less. No diabetic patient has come to my knowledge who has successfully withstood any operative procedure whose blood showed a combining power of less than 30 per cent. Based upon a considerable experience, it is my present opinion that with CO_2 of the blood plasma less than 35 per cent. an operation is too hazardous to attempt. Forty per cent. is the lowest figure that permits a reasonable margin of safety for surgical procedures, considering the superimposed acidosis consequent upon the course of infection and the anæsthetic.

Even when the acidosis estimation gives a satisfactory result, the

degree of hyperglycæmia cannot with safety be ignored. One sees many diabetics with no acidosis, but with a blood sugar over .35 per cent., who succumb to operations because of the acidosis that develops postoperatively. When the blood sugar is a higher figure than this at the time of operation a fatality is probable. One may say, then, that patients showing hyperglycæmia of over .35 per cent., or a CO_2 combining power of less than 40 per cent., cannot be expected to survive any operative procedure. The only safety with cases of this type is to change the metabolic state prior to surgical treatment. If there is not time to do this the case is hopeless.

At the other extreme are the cases with no acidosis and with blood sugar only twice normal, who survive operative procedures, even infections requiring surgical treatment, in a fairly high percentage. In all cases demanding surgical treatment, with the exception of emergencies, preoperative care is possible and, with the great majority, even with severe types of diabetes, the acidosis can be abolished and the hyperglycæmia reduced to a safe margin.

The treatment of patients with diabetes mellitus as a preparation for surgical operation requires a departure in no respect from recognized principles. The object of this treatment is the restoration of normal metabolism and the measure of success is the blood sugar and CO_2 of the plasma. There is but one primary means to this end, dietetic, and it is difficult for many to apprehend that in this disease food is a two-edged sword, and its use requires a nice scientific precision. In the first place, because the affections requiring surgical treatment are so frequently infections, and this infection predisposes to acidosis, attention to this factor is never subordinate. Symptoms of acidosis are protein in character and they can be anticipated by laboratory methods; then, too, radical changes in diet often produce a temporary increase of acidosis, which must be watched, and this is especially true in surgical cases. Although hazardous unless controlled by constant laboratory tests, fasting effects, with some cases, the most rapid decrease of hyperglycæmia and acidosis. Unfortunately, when infections of a surgical character complicate the primary diabetes, fasts are not infrequently accompanied by a rapid increase of acidosis. In the latter case there is no recourse except some form of nourishment. The diet at this juncture is determined by two considerations: (*a*) Fats are direct precursors of the ketone bodies and hence are contraindicated; (*b*) carbohydrates are being utilized scarcely at all by the body and therefore, if given, elevate the blood sugar and induce acidosis. This leaves only protein for food and this may be used as lean meat and eggs, with small amounts of green vegetables as a relish. The food intake should not exceed 300 calories daily at this period. In some instances a low diet such as described can be interpolated with fast days with benefit.

The use of alkalies in acidosis is general and the effect too often disappointing. When given by mouth it is essential to give large amounts—2 to 3 grammes (30–45 grains) an hour, until the CO_2 of the blood is raised to a safe margin. The soda is best given in Vichy water. Recently I have given soda bicarbonate emulsified in olive oil subcutaneously—10 to 15 grammes of soda in 10 c.c. of oil.[1] Attention to a copious fluid intake and catharsis is important here, as in uræmia.

This brief statement of the principles and methods gives an outline of the treatment which must be adapted to particular exigencies as they occur. Some patients with moderately advanced diabetes can, by treatment of this type, be carried through operative procedures, but not all. Some, especially those with virulent infections of the cellulitis type, do not respond to any method or procedure.

On the other hand, when the complication which requires surgical treatment is not an infection, it may not be excessively difficult to reduce the hazard incident to diabetes very considerably. The successful amputation of the breast for carcinoma, complicating moderately severe diabetes, illustrates the point. Infections, however, remain the chief problem and the operations should be considered with the care accorded to brain tumors.

[1] A suggestion of my colleague, S. R. Benedict, Professor of Chemistry.

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ARTERIOSCLEROSIS:

THE THREE-FOLD MENACE OF THE PRESENT DAY.*

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So much confusion exists in the minds of medical students, hospital internes, and the profession generally, about the clinical differences between arteriosclerosis and atheroma, that an attempt will be made in this discussion to clarify the situation. This is particularly important at the present time, when the stress and strain of urban life has been intensified during the past three years by the demands made upon our people by the incubus of the great World War, and the subsequent social, financial and industrial unrest caused by that cataclysm. Life in this city has always been strenuous enough, but recent events, with their train of disaster and death in many families, with the increased cost of living, and with the mounting difficulties of procuring labor for the development of our food and industrial resources, have made demands upon the

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nervous systems of our people greater than the demands of any other period in our history.

It is a military axiom that success in war is not a question of men and money, but of bread and meat. An army marches upon its stomach, and its commissary department must functionate with 100 per cent. efficiency. The history of our Spanish-American War, of the British-Boer conflict, of the Russo-Japanese affair, thoroughly demonstrated this, and emphasized to our Government its prime necessity, when four millions of men and women were transported over three thousand miles of water, amid submerged perils. By the genius and business ability of distinguished civilian and military men, these men and women were kept surrounded not only with necessities, but with comforts. In the human body there are many times four millions of living cells, actively and constantly engaged in warfare against the natural march of decay, and against the unnatural and insidious invasion of disease germs. How shall we maintain our commissary department at the highest notch? It is purely a question of air and food supply. Technically it is called the physiological processes of nutrition. In health, a perfect commissary department is supplied by the heart and blood-vessels. They constitute its purveyors. They not only distribute the food where needed, but with an intelligence conferred by the Infinite Giver of all wisdom, they deliver to each individual ultimate cell of the many billions, the exact kind of selective material needed for its renewal, and, at the same time, remove its waste for excretion by the proper channels. This elementary sketch of the physiology of nutrition may be tiresome to this professional audience, but is well to bear in mind. Do we always try to conserve this

wonderful mechanism? Do we stop in our mad rush for preferment, fame, and wealth to consider the vast amount of work done without our conscious intervention by the heart and blood-vessels under the guidance of the involuntary nervous system? The normal heart beating at 72 times per minute, ejects an amount of blood at each systole which requires a force estimated at two foot pounds, to move along the column of blood ahead of it; 144 foot pounds per minute makes an aggregate of over 100 tons of work in each 24 hours, and this is only the minimum, with the body at rest. To sustain this strain we must have a system of vessels which are not merely inert tubes for the conduction of blood, but living vital tissues, a living part of a living whole. It is not remarkable that cardiovascular degeneration occurs so often. It is only remarkable that it does not occur oftener, before man has reached the Biblical three score and ten. Cardiovascular degeneration is especially the harvester of death for medical men, from its three-fold results of nephritis, apoplexy, and heart disease. Statistics compiled some years ago showed that the death rate among medical men from these causes was exceeded only by that of saloonkeepers, butchers, quarrymen, and factory operatives. I therefore offer no apology for bringing this subject to your attention, but only the hope that it may help you to keep your own days long in the land.

I will not inflict upon you any detailed description of the anatomy of the heart or arteries. Studies by recent instruments, supposed to be more precise in their yield of information than were the educated fingers of our revered predecessors at the Bellevue bedsides, have taught us much as to the physiology and pathology of the heart in action, and have

helped us to realize the truth of the old axiom, that a man is as old as his arteries. These studies may help, some day, to point the way for man to keep his arteries as young as he would like them to be, and may help our patients to rid themselves of that bugbear which is called arteriosclerosis. This terrifying term lacks the satisfying unction of "that blessed word Mesopotamia," in the Highland lady's system of theology, but is just as mysterious to the laity. What is arteriosclerosis? Is it a "disease," or an effect of diseases, many and various? How does it differ from atheroma?

Definition.—Arteriosclerosis is a hyaline degeneration of the structural elements of the arterial wall, with connective tissue substitution, hyperplasia, and subsequent contraction with induration, whereby the characteristic functions of the vessel wall—retention, absorption, metabolism, with the power of extension and contraction, are weakened or lost.[2,3] It is a pathological condition, and may arise at any age, in early life, in childhood, or even in infancy. Atheroma, on the other hand, is the usual accompaniment of advancing age, and is a physiological condition. At the post-mortem table both conditions may be found in the same subject, hence the confusion that occurs in our minds. Even Osler, usually an apostle of clarity in teaching, includes arteriosclerosis and atheroma in one definition.[4]

Pathology.—In the aorta and its large branches there is much elastic tissue and relatively little muscle. As the arteries approach the organs to which they are distributed, this proportion changes, so that the supply of blood may be increased or decreased as needed. Hence it is in the arterioles or smaller arteries that the lesions of arteriosclerosis do the

most damage. Pathologically we find four types of lesions: (1) nodular; (2) diffuse; (3) senile; (4) syphilitic. In advanced arteriosclerosis all types or grades may be found. The nodular form is found particularly on the aorta and large vessels, especially at or near the orifices of branching vessels.

In the diffuse form the whole arterial system is rarely, if ever, attacked uniformly. We may have pipe-stem radials with a smooth aortic lining, but with enlargement of the aorta and thinning of its coats and loss of elasticity. The senile type leads eventually to calcareous deposits in the intima, with widened, elongated, inelastic aorta.

In syphilitic aortitis, plaques form which, instead of undergoing an atheromatous change, as in the nodular form, are prone to scar formation with puckering. *Spirochetæ pallidæ* have been found in the degenerated media, and in small gummata beneath the intima. The Wassermann reaction should be tested in every case of aortic insufficiency, and the pulse pressure reading carefully recorded. In the smaller arteries and arterioles three kind of changes occur: A muscular hypertrophy; a fibrosis of all the coats; or a marked proliferation of the intimal endothelium, leading in time to endarteritis obliterans. Other poisons than syphilis can produce the same set of changes, the essential lesion in the large arteries being a degeneration of the middle coat, followed by an hypertrophy of the intima, layer upon layer being added in an attempt to restore the strength of the vessel. The results of experiments, upon rabbits and dogs, to produce arteriosclerosis by injection of adrenalin, barium chloride, digitalin, physostigmine, nicotine, and other drugs, as well as by feeding animal proteins to

rabbits, have been very discordant, and have not added much to our knowledge of the subject. The toxins of the typhoid bacillus and the *Streptococcus pyogenes* have produced changes somewhat analogous to the intimal proliferations found in the human aorta, thus confirming the clinical observations of Thayer and others that individuals who have had typhoid fever have more palpable arteries than other individuals of equal age.

Etiology.—There are various causes for arteriosclerosis, such as heredity, age, sex, alcohol, venereal disease, rheumatic fever, other acute infections, high living and hard work. While the devotion of doctors is primarily given at the shrine of Minerva, and not at those of Venus and Bacchus—although the latter is now only a source of wistful archæological study, the doctor must make also the anvil of Vulcan ring, not literally with hammer and spark, but with the constant impact, upon the billions of the functional nerve-cells of his brain, of the woes and worries of his patients, of the increasing demands of his landlord, and of the tire-troubles of his vehicle. The influences of heredity we cannot forestall, since we are not allowed to be judicious in the selection of our ancestors, but we can minimize the damage by avoiding their mistakes. Age is something that nightly pitches our moving tent a day's march nearer home, but if we travel with a contented mind, and a little faith that the road, whether we believe that it leads over Mt. Sinai or over Mt. Calvary, finally stops at the Father's house, we can laugh at the old gentleman with the exuberant whiskers and the rusty scythe who marched by our side. The influence of sex disparity in producing strain will probably lessen as the world goes on, now that our beloved sisters stand

side by side with us in the marts of trade, in the ranks of professions, on the battle field, and in the direct primaries. Alcohol is likewise a fading specter, since a clamorous minority have dictated to the medical profession how they shall not treat pneumonia, septicemia, and other acute infections, but leaves to the old soak his accustomed sources of underground supply, without the necessity of a prescription with a ten-day limit for each pint; still, for the well-to-do, who find the call of the wild too urgent, George Bernard Shaw points out that there is a free country only seven days away. Syphilis is the predominating factor in arterial degeneration in the young, and may attack any of the three walls of the vessels, affecting the brain by preference because syphilitic arteritis is localized in arteries supplied with lymphatic sheaths. The conditions that keep up high blood tension, such as the endogenous poisons of perverted metabolism in gout, diabetes, chronic nephritis, and obesity, all lead to arterial thickening and subsequent degeneration.

Overeating, that is to say, food in excess of work and excretion, is another potent cause, causing the hyperemia, or hyperpiesia, so well described by Sir Clifford Allbutt.[5] Allbutt was one of the first to point out that not all cases of arteriosclerosis are attended by high blood pressure. He makes three classes, viz.: (1) high pressure arteriosclerosis; (2) involutionary or decrescent (senile); (3) infectious or toxic. Allbutt believes that there are two modes of hereditary transmission, the direct and the indirect; the direct consisting of an original frailty or toxic susceptibility which may run in families; and the indirect, which apparently depends upon a proclivity to some ill-understood poisoning or perversion. He insists that arteriosclerosis is not

a disease, in the sense in which we speak of tuberculosis or pneumonia as a disease, but in reality is an effect of many and various diseases. Warfield[6] emphasizes the same point, but considers that syphilitic arteritis may be viewed as an entity, because the cause is known and the lesions are characteristic. Mental strain, except in those care-free persons who laugh their way through life, is a frequent cause. It is not the work, but the worry, that results in high tension, arterial strain, compensatory thickening, and hypertrophied heart. Muscular over-work, especially when combined with alcohol and coarse heavy food, is frequently seen as an operating cause among the laboring class, both whites and negroes, but especially among the latter. Renal disease, especially the contracted red kidney, or the clinically shrunken and scarred kidney, the so-called arteriosclerotic kidney, may be either causative or resultant. He who predicts, however, from the results of uranalysis, what type of kidney will be shown at autopsy, is rushing in where angels might fear to tread. Functional response of the kidney, as shown by appropriate tests, is a better guide than pathological classification. Endocrinology is at present fascinating its followers as being the responsible agent in this, and in almost all diseases. The current literature abounds in speculative and imaginative theories and explanations, but this hay is often a little high for the short horses.

Symptomatology.—The story of arteriosclerosis must go back a long way, perhaps even into the third or fourth generation. So much of it depends upon the quality of arterial tissue inherited that a careful family history is desirable. Next the personal habits and history of previous diseases must be elicited. It is doubtful that sclerosis itself would

produce recognizable symptoms or physical signs, did not the diseased arteries fail to carry a sufficient supply of blood to the various organs and in that way cause derangements of function. Hence the clinical picture varies, according to the organ primarily or chiefly affected. Thus we may have symptoms referable to the general system, or local manifestations pointing to nervous, cardiac, renal, abdominal, or peripheral arterial mechanisms. Manifestly a condition of so protean a nature cannot be briefly described. The symptomatology sometimes makes the diagnosis easy and certain, sometimes only presumptive, sometimes impossible. Well developed arteriosclerosis shows four pathognomonic signs: hypertrophy of the heart; accentuation of the second aortic sound; palpable thickening of the arteries; heightened blood pressure. All need not necessarily be present to establish the diagnosis. Prior to the development of these changes, minor alterations in the various functions of the body must be patiently sought for, in the light of the well known etiological factors. Periodical examinations, of subjects who believe themselves to be entirely well, are of great benefit in uncovering those minor manifestations of disease which taken at the flood lead back to health, but neglected, voyage ahead to irreparable damage. A detailed recital of all such changes would transcend the limits of your patience. The value of careful blood pressure studies, especially studies of the pulse pressure, cannot be too often insisted upon, but blood pressure readings, like Opie's colors, must be mixed with brains to be useful guides. Hypertension itself is practically always a compensatory process, and should be regarded as one regards a compensated heart lesion. It may be not only essential,

but actually life saving, but, when it tends to increase, we must try to reduce it.

Diagnosis.—A good history is half the diagnosis; in some instances the whole diagnosis. Supplementing this by careful bidigital palpation of the arteries, by correct interpretation of the blood pressure readings, by accurate estimation of the heart's size and power, and by direct ophthalmoscopic inspection of the retinal vessels, a diagnosis can usually be established. The ophthalmoscope especially is useful in early diagnosis and shows changes which may not only be suggestive but even pathognomonic.[5] In the young, hereditary influences play an important role, a history of syphilis insufficiently treated, or of the abuse of alcohol, in the family history being particularly significant, as is also a history of gout and rheumatism. Among the infectious disease, the story of a long siege of typhoid fever bears great weight. Severe prolonged laborious occupation, or mental strain, should be carefully considered. I do not believe that the use of tobacco in moderation is especially deleterious, even though it has been experimentally demonstrated that the smoking of one cigar after dinner entails a loss of 20 per cent of the energy provided by a good dinner.

Differential Diagnosis.—This requires the exclusion of pseudo-angina pectoris, true angina pectoris, peptic ulcer, appendicitis, or other inflammatory abdominal conditions. Warfield[6] gives the following differential tables:

PSEUDO-ANGINA PECTORIS	TRUE ANGINA PECTORIS
Etiology rather uncertain; hysteria, neurasthenia, toxic agents, and reflex conditions.	Etiology not certain, but almost always associated with arteriosclerosis of the coronary arteries, and also aortic regurgitation.
No age is exempt; usually in young people, especially females.	Age is important. Rare before forty, and males usually affected.
Paroxysms of pain occur spontaneously, are periodic, and often nocturnal.	Paroxysms brought on by overexertion or excessive mental emotion. Rarely periodic.
Pain, while severe, is diffuse and sensation is of distention of the heart. No sense of real anguish.	Intense pain, radiating down the arm; heart felt as in a vise. Sense of anguish and impending dissolution.
Duration may be an hour or more. Restlessness and emotional symptoms of causative conditions are prominent. Usually no increase in arterial tension. Prognosis favorable.	Duration from few seconds to several minutes. Silent and fixed attitude, rigidity rather than restlessness. Arterial tension as a rule increased. Prognosis most unfavorable.
PEPTIC ULCER.	ANGINA ABDOMINALIS.
Occurs as a rule in young persons, most often females.	Occurs only in adults over forty who have been heavy eaters and drinkers, mostly males.
Pain of boring character, increased by food and by certain positions with reference to stomach. Felt through to left of spine. Occult blood found in stools. Considerable anemia apt to be present. Arterial tension usually low.	Pain, cramp-like, diffuse, but more localized in epigastrium. Not necessarily connected with food. No occult blood in stools. Anemia often absent. Arterial tension high (splanchnic sclerosis).

Prognosis.—In a disease so variable in its manifestations, an accurate prognosis is no easy matter. The chief factors to be considered are: (1) the site of the sclerosis; (2) the probable stage; (3) the existing complications, and (4), last and most important, the patient himself, his habits, his character, and his mode of life. In any event, the prognosis should be most guarded. In the cardiac form, angina pectoris, apoplexy from cerebral hemorrhage or embolism or thrombosis, may supervene without warning. In the arteriosclerotic kidney, uremia may develop from slight indiscretions or without assignable cause. When the disease is localized in the peripheral arteries, gangrene may result, or the minor but uncomfortable seizures of Raynaud's disease or erythromelalgia. The cerebral type with its early dizziness, dullness, inability for mental concentration, and mental irritability should put us on our guard. Intestinal hemorrhage is a grave sign, as an indication of splanchnic sclerosis, possibly leading to embolus or thrombus of the superior mesenteric artery, or in smaller branches to necrosis and ulceration of the intestine.

Prophylaxis.—Decay and degeneration of tissues are necessary accompaniments to the song of life, and none of us can escape growing old. We cannot prevent the heart from beating out its 100 tons of work a day, nor relieve the arteries of their strain. Yet with the inheritance of a healthy organism and proper care of his machinery, comparative anatomy and physiology would allow man a duration of life equal to that of the one-hoss shay. Herbert Spencer's definition of life is that it is "the continuous adjustment of internal relations to external relations." This means that we must get the maximum amount of work done with

the minimum amount of wear and tear on the vessels. In these strenuous times, this is difficult, but not impossible. It is not the work, but the worry, that leads to arterial degeneration. Work, with a contented mind, moderate appetites, and modest ambition, will strengthen and develop rather than weaken the bodily forces. Excesses of any kind, be they mental, moral, or physical, tend to wear out the organism. Judicious exercise and well chosen diet are the principal things to discipline ourselves about. Successful doctors complain that they have no time for physical exercise, such as walking, but prefer the lolling luxury of a limousine while making calls. Alonzo Clark who walked and worked until his eighty-fourth year, remarked that when a doctor needed a horse to pull him around he must be weak in the legs, and if he needed two horses, he must be weak also in the head. The city doctor's horse has disappeared, to give place to the rapidly moving automobile, and to encourage obesity and lead to Sir Clifford Allbutt's hyperpiesia. Such are the sweets of prosperity. Every man and woman over forty years of age should have the equivalent of four miles walking in the open air every day. Given sound heart and lungs, this will occupy about one hour. If they have the opportunity to visit the neighboring golf links, and do this walking over an eighteen-hole course of springy turf, with the additional training of the eye and hand and of the control of temper which comes with the mastery of the elusive pill, so much the better. The nineteenth hole now lives only in mournful retrospection. Scholastic philosophy teaches that the chief end of man is happiness; not merely pleasure, for pleasure only depends upon the possession of things, and things de-

cay; not joy, for joy depends upon the possession of friends, and friends die; but spirituality, which depends upon the possession of character, and character is immortal. Old age does not invariably lead to hardening of arteries. A patient of mine, who wrote at least one book every year until her eighty-fifth year, and the spirituality of whose writings has been a comfort and solace to millions of readers, had the soft arteries of a woman of thirty, and a blood pressure of 120.

Treatment.—It is manifest from what has been said that there is no routine plan of treatment for an essentially chronic progressive disease like arteriosclerosis. The keynote is individualization, study of the patient with the disease. This cannot be learned from reading text-books or journal articles, nor even taught at bedside clinics. Teachers can only teach what they are, not what they know. Our old friends, general principles, can be given in the way of advice, by way of prophylaxis, provided we catch the patient early enough in life. After that, it will depend upon our personal influence over the patient, and his own stability of character, whether we can correct the injurious influence of his environment. Every man is more or less the arbiter of his own fate. The one essential in the diet for a patient is reduction in the amount. Americans eat too much, as a rule, but those who have traveled in German and Scandinavian countries will admit that by comparison we are abstemious, if not penurious, eaters. Meat has been so abundant in this country that few meals are considered complete without an abundance of meat and sweets. Herbert Hoover deserves the everlasting thanks of this generation, even though he be denied their votes. A diet of vegetables, fruit, fish, bread

and butter, and milk, with very little meat, will suffice in most cases. The supposed injurious effects of the lime salts in milk can be avoided by the addition of lime water, which precipitates the soluble lime salts in the stomach, and facilitates their excretion by the intestines rather than by the kidneys. Buttermilk, either from the churn or from the *Bacillus acidus lacticus*, may furnish an agreeable substitute for sweet milk. Balneotherapy demands careful individualization also. Our generation is certainly a bathing one, but it is folly to encourage the morning cold bath to those who do not react glowingly after it, and criminal to advise the Turkish or Russian bath to one with degenerated cranial arteries.

The one drug to which we turn, for the prescription which most patients expect in return for the fee, is iodide of potassium. Its action has been the result of much controversy. Some writers believes that it acts as a vasodilator and thus decreases blood pressure. Others that it lessens the viscosity of the blood. Capps[9] denies that it does either and says that its only benefit is selective absorption of the cellular exudate in syphilitic arteritis. Lemoine[10] believes that iodide of potassium is a therapeutic heresy. C. T. Hood[11] states that it is now generally conceded that iodides and iodine have no place in the treatment of hypertension or arterial fibrosis. His own hypothesis is that salt-poor and salt-free diet should be pushed to the point of removal of the surplus sodium chloride from the body, and to keeping the tissue sodium chloride content at the physiological amount. To help to accomplish this he advocates administering one per cent solution of potassium nitrate of which fifteen drops are to be taken three times a day in half a

glass of water until the individual is filtered of his excess chlorides.

Long before the endocrinists held their present sway, it was believed that the thyroid secretion and that of the adrenals were antagonistic, and small doses of thyroid extract, half a grain twice a day, were given with benefit to reduce hypertension. But it is not always wise to reduce hypertension. It is perhaps fortunate that our well meant efforts to accomplish reduction do not always succeed. Nitroglycerin will usually fail, as it is eliminated in about thirty minutes. Sodium nitrate will hold a slight effect for about two hours. There is no question about the efficacy of amyl nitrite in anginal attacks, and many elderly patients of mine are profuse in their verbal expressions of gratitude for its presence at their bedsides at night, or in convenient vest-pocket pearls by day. Benzyl benzoate has recently been lauded by Macht in angina, and in other spasmodic seizures. I would put tincture of aconite into the hands of a careful nurse, or hospital interne, for use in excessive hypertension, but would want the effects carefully watched, and the results checked by the sphygmomanometer. But the greatest good is done for our patients in Bellevue and St. Vincent's by absolute rest in bed. Karell diet for four days, hot packs, and free purgation, with venesection added in uremic convulsions or coma. Morphine is sometimes invaluable to secure rest at night, but it should never be forgotten that morphine checks all the secretions but one, and that the habitual use of morphine is the beginning of the end. Influenced by the teachings of the late George L. Peabody in the New York Hospital, I have made extensive trial of amylene hydrate in hot milk at bedtime. Some patients swear by it,

many others swear at it. It can be given by rectum when the stomach is intolerant. The Trunecek serum has gone the way of all fads. The treatment of the later stages of arteriosclerosis becomes that of the damage done in brain, heart, kidneys, or intestines, and opens up too wide a field to be covered in this discussion. Prevention, by recognizing the disease in its early stages, must after all be our watchward. Of the 73,266 deaths in the city of New York in 1912, 7251 occurred from organic diseases of the heart; 7104 from nephritis, and from cerebral hemorrhage and softening 2805.[8] In the total registration area of the United States, approximately 23.2 per cent occurred from these causes. The percentage in the rural districts alone was 26.7, thus showing that the urban mortality is less than that of the rural. This is contrary to the usually accepted opinions of the back-to-the-soil prophets.

New York State has a slightly better showing, the tables of the combined cities of the Empire State giving a rate of 20.5 per cent of the total mortality, while the rural portions furnished figures of 22.3 per cent.[9] New York physicians may therefore lay this flattering unction to their souls, even though the City of New York does not measure up to its vaunted standard of excellence in hygiene and sanitation. Other tables will show that this disproportionate loss of life occurs during the ages of from thirty to sixty years, the period of greatest productivity. It is improbable that therapeutics will work wonders in decreasing this mortality for many years to come. Still we must labor to increase our efforts at "preventability." Preventability is defined by Irving Fisher, in the report of the National Conservation Commission

on National Vitality, as follows: "A ratio of preventability is the fraction of all deaths which would be avoided if knowledge now existing among well informed men in the medical profession were actually applied in a reasonable way and to a reasonable extent." The practical meaning of this is that we should instruct our patients in the underlying etiological factors of this group of diseases. Such a scheme of instruction would include the elaboration of plans for the elimination or control of contagious and infectious diseases, for the elimination or control of conditions causing poisonings and intoxications, for the supervision and regulation of conditions inducing abnormal physical strains, and for minimizing the mental stress of the community.[9]

Along this road, social service and social hygiene are making steady headway, but the way is long and rough, and we who are traveling it can only lend a hand to those others who are weary and heavily laden, to make smooth the path for them. I commend to your earnest attention the comprehensive plan outlined by Ira S. Wile in the MEDICAL RECORD for June 5, 1915, which well deserves our careful study and active cooperation. If "health is purchasable" as alleged by our Health Departments, its cost, in these days of luxurious extravagance, should not be a deterrent. Dr. Wile's scheme may sound Utopian, and difficult of accomplishment at the present time, but if we all bend our backs to the task, it may come about in the present generation.

"We are all weary travelers along Life's dusty way,
If any man can play the pipes, in God's name let him play."

REFERENCES.

1. Eichborg, Joseph: *Philadelphia Medical Journal*, March 10, 1900, p. 585.
2. Whittaker, J. T.: American System of Practical Medicine, Loomis-Thompson, vol. ii.
3. Adler, Isaac: Experimental Arterial Disease, *Am. Journal Med. Science*, August, 1905, p. 241.
4. Osler, William: Modern Medicine, edition 1908, p. 429, vol. iv.
5. Allbutt, Clifford: Diseases of the Arteries, Macmillan, London, 1915.
6. Warfield, L. M.: Arteriosclerosis, Third Edition, 1920.
7. Goodall, Strickland: MEDICAL RECORD, April 25, 1914, p. 762.
8. Capps, J. A.: MEDICAL RECORD, October 26, 1912, p. 774.
9. Wile, Ira S.: MEDICAL RECORD, June 5, 1915, pp. 925-930.
10. Lemoine, G.: *Gazette des Practiciens*, September 1, 1913, reviewed in MEDICAL RECORD, October 4, 1913, p. 622.
11. Hood, C. T.: MEDICAL RECORD, August 14, 1920, p. 280.

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CLINICAL CALORIMETRY

XXIX. THE METABOLISM IN TUBERCULOSIS *

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INTRODUCTION

In regard to the dietary of tuberculous patients medical opinion has fluctuated within wide limits. The extent of this fluctuation may be seen by an examination of the data collected by Fisher,[1] regarding the dietaries given patients by ninety-five of the leading sanatoriums of the world. In this list the total number of calories fed daily ranges from a maximum of 5,500 to a minimum of 2,140. The number of grams of protein varies from 60 to 190 per diem. To the practical physician, who is faced with the problem of selecting the best type of dietary to prescribe for tuberculous patients, the problem is quite bewildering. To make the selection it is necessary to know, first, the total energy transformations in such patients and, second, the extent of destruction of protein by the toxins of the disease and the minimum amount of protein which must be given to maintain the patient in nitrogen equilibrium. A search of the literature for this information yields unsatisfactory results because of the meagerness of the data and of the fact that most of the work was done before the advent of the most accurate methods of study.

HISTORICAL

For a very complete and comprehensive compilation of the work done prior to 1903 one may refer to Ott.[2] A great part of this work, in which it appears that the technic used was crude and experimental conditions poorly controlled, will be omittted in our references. Some of it is of great historical interest, as for instance, the work of Nysten[3] carried out in Paris in 1811. By means of a respiratory valve he separated the inspired from the expired air, which he collected in a bladder during a measured period of time. This air was analyzed

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† During 1916-1917 Dr. Wm. H. Olmstead of St. Louis assisted in the work.

1. Fisher, Irving: Proc. Sixth Internat. Congr. on Tuberculosis **1**:694, Part 2, 1908.

2. Ott, A.: Die chemische Pathologie der Tuberculose, Berlin, 1903.

3. Nysten: Ueber die chemischen Atmungserscheinungen in Krankheiten, Meckel's Deutsch. Arch. f. Physiol. **3**:264, 1817.

for carbon dioxid by shaking it with lime water (over mercury in a graduated cylinder), the oxygen then being absorbed by phosphorus. Calculation of the energy transformation from the gaseous exchange could not be done at that time, but the physiologic principle is the one most commonly used today. This work is most significant when one considers that it was contemporary with the development of percussion of the chest by Auenbrugger, and the invention of the stethoscope by Laennec.

Although the physical diagnosis of the disease progressed by leaps and bounds, the next study of the respiratory exchange was not made until by Hannover,[4] who studied the production of carbon dioxid in five patients with phthisis. The body weight is given and the carbon dioxid per minute. By assuming an average respiratory quotient of 0.80, we may calculate the daily heat production of these patients as between 1,200 and 2,100 calories per day, and from 26.5 to 40 calories per kilogram of body weight. In 1878 Moeller [5] studied three poorly nourished patients with phthisis, males weighing from 44 to 45 kg., aged from 24 to 48 years. The carbon dioxid produced was measured in the Pettenkoffer-Voit apparatus in six hour periods. These patients all had food and beer, so that the metabolism was not basal. Assuming an average respiratory quotient of 0.80, the daily heat production would be between 1,600 and 1,780 calories, or from 35 to 40 calories per kilogram of body weight.

The first work in which the finding of normal respiratory quotients may be taken as evidence of good technic is that of Loewy,[6] who studied exchange of oxygen and carbon dioxid, minute volume respired and nitrogen excretion at different body temperatures after tuberculin injections, using the Zuntz-Geppert appparatus. He found that there was only a moderate increase in oxygen consumption in fever and that it was greater with rising than with falling temperatures. In three of his cases, which were incipient, the minute volume respired increased slightly, but in a fourth case with extensive tuberculosis there was a rather close parallelism between the oxygen consumed and the minute volume. This observation is one of extreme practical importance, as will be seen later.

In the same year Kraus and Chvostek [7] studied five phthisical patients with a Zuntz-Geppert apparatus. In some of the cases the

4. Hanover: De quantitate relativa et absolute acidi carbonici ab homine sano et aegroto exhalati, Copenhagen, 1845, p. 82.

5. Moeller: Kohlensäureausscheidung der Menschen bei verkleinerter Lungenoberfläche, Ztschr. f. Biol. **14**:542, 1878.

6. Loewy, A.: Stoffwechseluntersuchungen im Fieber und bei Lungenaffectionen, Virchow's Arch. f. path. Anat. **126**:218, 1891.

7. Kraus and Chvostek: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Tuberculininjection, Wien. klin. Wchnschr. **4**:104, 127, 1891.

respiratory quotients lie beyond the limits of possibility. These are the first investigators to give the height of the patient so that the surface area may be calculated. The conditions were not basal, as the patient was not fasting. However, calculations show that an increase of 39 per cent. in the metabolism increased the minute volume respired from 7,743 c.c. to 10,000 c.c., in a case in which proper quotients were obtained.

Work done by Speck [8] may be mentioned also, since it shows in many cases a marked parallelism between the amount of carbon dioxid produced and the minute volume. The respiratory quotients are either so low or so high as to make the results of doubtful value. Data relative to the amount of food taken and muscular activity are not given. Robin and Binet [9] give mass statistics regarding the minute volume, lung capacity, oxygen consumption and respiratory quotients of 162 phthisical patients. Averages only are given, the methods used are not stated, and there has been no attempt to compare individual patients with normals of the same size, so that the data are not very satisfactory. However, it is of interest to note that the minute volumes respired were from 80 to 110 per cent. greater than those of the normals studied. They also found a consumption of oxygen from 70 to 100 per cent. greater. The respiratory quotients were lower in the tuberculous patients. Lung capacity was also greatly reduced.

Staehelin [10] studied a tuberculous patient during a night sweat in a Jacquet respiration chamber. Food was taken before the observation and the subject was very restless. He concluded, however, that the metabolism was not raised and that sweating had no influence on the total metabolism.

In a recent study of the effect of acetyl salicylic acid on the heat regulation in fever Barbour [11] used three tuberculous subjects. These subjects were studied in a Benedict respiration chamber under basal conditions. The basal metabolism in these three cases was only from 3 to 4 per cent. above the average normal.

The absorption of food in tuberculosis has been studied by Blumenfeld,[12] who found that the percentage losses of nitrogen and fat in the stools were within normal limits. However, in certain cases there was marked interference with absorption. Biedert [13] reported a case

8. Speck: Physiologie des menschlichen Athmens, 1892.

9. Robin and Binet: Bull. méd. Par. **15**:249, 1901.

10. Staehelin, R.: Der respiratorische Gaswechsel eines Phthisikers während des Nachtschweisses, Ztschr. f. klin. Med. **66**:241, 1908.

11. Barbour, Henry G.: Arch. Int. Med. **24**:624 (Dec.) 1919.

12. Blumenfeld, F.: Ueber die diaetetische Verwerthung der Fette bei Lungentuberculose, Ztschr. f. klin. Med. **28**:417, 1895.

13. Biedert: Die Tuberculose des Darms und des lymphatischen Apparats, Jahr. f. Kinderh. **21**:172, 1884.

TABLE 1.—Alcohol Checks for 1916-17

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat			Oxygen			Carbon Dioxid			Water			R. Q. Theory 0.667
			Theory, Cal.	Found, Cal.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	
5/17/16	1	13.49	87.63	87.20	−0.5	25.80	26.35	+2.1	23.65	23.34	−1.3	15.47	16.09	+4.0	0.644
92.92	2	13.26	87.23	87.41	+0.2	25.69	24.75	−3.7	23.55	23.34	−0.9	15.40	15.91	+3.3	0.686
	3	13.72	90.26	89.24	−1.1	26.58	26.29	−1.1	24.36	23.90	−1.9	15.93	16.26	+2.1	0.661
Average	...	.....	88.37	87.94	−0.5	26.02	25.80	−0.8	23.85	23.59	−1.1	15.60	16.09	+3.1	0.665
10/3/16	1	12.05	79.27	82.02	+0.9	23.34	23.31	−0.1	21.40	21.42	+0.1	13.99	15.14	+8.2	0.668
92.92	2	12.78	84.07	86.45	+2.8	24.76	25.05	+1.2	22.69	22.57	−0.5	14.84	15.76	+6.2	0.655
Average	...	.....	81.67	84.24	+3.1	24.05	24.18	+0.5	22.05	22.00	−0.2	14.42	15.45	+7.2	0.662
10/10/16	1	12.83	84.41	83.51	−1.1	24.85	24.93	+0.3	22.78	22.42	−1.6	14.90	15.27	+2.5	0.654
92.92	2	13.16	86.57	87.08	+0.6	25.49	24.94	−2.2	23.37	23.42	+0.2	15.28	15.79	+3.3	0.683
	3	13.36	87.89	85.42	−2.8	25.88	25.88	0.0	23.72	23.39	−1.4	15.51	15.76	+1.6	0.657
Average	...	.....	86.29	85.34	−1.1	25.41	25.25	−0.6	23.29	23.08	−0.9	15.23	15.61	+2.5	0.665
12/4/16	1	11.97	78.75	80.57	+2.3	23.19	22.63	−2.4	21.25	20.92	−1.6	33.90	31.40	−7.4	0.672
92.92	2	11.68	76.84	77.80	+1.2	22.63	22.37	−1.4	20.74	20.78	+0.2	33.57	30.89	−8.0	0.676
	3	11.33	74.54	76.88	+3.1	21.95	21.21	−3.4	20.12	19.67	−2.2	33.16	30.63	−7.6	0.674
Average	...	.....	76.71	78.42	+2.2	22.59	22.07	−2.3	20.70	20.46	−1.2	33.54	30.97	−7.2	0.674
2/28/17	1	11.94	78.14	78.15	0.0	23.01	22.66	−1.5	21.09	20.61	−2.3	13.85	14.39	+3.9	0.662
92.44	2	11.91	77.95	78.32	+0.5	22.95	22.18	−3.4	21.04	21.09	+0.2	13.83	13.62	−1.5	0.691
	3	12.12	79.32	80.64	+1.7	23.36	23.13	−1.0	21.41	21.19	−1.0	14.06	14.37	+2.2	0.666
Average	...	.....	78.47	79.04	+0.7	23.11	22.66	−2.0	21.18	20.96	−1.0	13.91	14.13	+1.6	0.675
4/23/17	1	12.62	82.59	82.93	+0.4	24.32	23.01	−5.4	22.29	21.47	+3.7	11.64	14.58	−0.4	0.678
92.44	2	11.39	74.54	75.36	+1.1	21.95			20.12			13.22	13.83		
	3	13.40	87.70	87.98	+0.3	25.82	46.92	−1.8	23.67	42.92	−2.0	15.55	15.45	+1.8	0.665
Average	...	.....	81.61	82.09	+0.6	24.03	23.31	−3.0	22.03	21.45	−2.6	14.47	14.62	+0.6	0.669
Totals.....	.....	.....	1397.70	1406.96	+0.7	411.57	405.61	−1.4	377.25	372.45	−1.3	307.10	305.14	−0.6	0.668

* 20 gm. extra water introduced

of fat diarrhea in a child with tuberculosis of the intestine, mesenteric lymph nodes and peritoneum. Also Friederich Mueller[14] found a loss of 32.9 per cent. of fat and 7.9 per cent. of nitrogen in the stools of a patient with tuberculous ulcers in the intestine and marked amyloidosis which involved the liver very slightly and the pancreas not at all.

The question of the toxic destruction of protein has received much attention. An excellent compilation of this work, with abundant quotations of experimental data, may be found in Ott.[2] The general results of this work tend to show that in the afebrile condition many phthisical patients will readily make large gains in nitrogen. With febrile patients, either with spontaneous fever or with fever following tuberculin injections, small losses of nitrogen occur on diets furnishing about 2,500 calories and from 100 to 150 gm. of protein per diem. These small nitrogen losses would become important only because of the long duration of the disease. The determination of the protein minimum in tuberculosis does not seem to have been made, although it has been the subject of some speculation.

The discussion of the nitrogen losses in phthisis would be incomplete without mention of loss in the sputum. Lanz[15] estimated the daily nitrogen loss in the sputum of sixteen patients with phthisis. The protein loss was calculated from the total nitrogen of the sputum and varied from 1.69 to 7.00 gm. of protein per diem.

METHODS OF STUDY

The respiration calorimeter of the Russell Sage Institute of Pathology was employed. This apparatus has been previously described in Paper 2 of this series.[16] The technic has been essentially that described in Paper 4 of the series,[17] with the few exceptions noted below. Patients were studied 14 to 16 hours after the last regular meal, though each received the small standard breakfast described in Paper 26 of this series.[18] The only effect of this meal was found to be an increase in the metabolism of 2 per cent. in the third hour

14. Mueller, Fr.: Untersuchungen über Icterus, Ztschr. f. klin. Med. **12**:86, 1887.

15. Lanz: Deutsch. Arch. f. klin. Med. **56**:619, 1896.

16. Riche, J. A., and Soderstrom, G. F.: The Respiration Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital, Arch. Int. Med. **15**:805 (June) 1915.

17. Gephart, F. C., and Du Bois, E. F.: The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (June) 1915.

18. Soderstrom, G. F., Barr, D. P., and Du Bois, E. F.: The Effect of a Small Breakfast on the Heat Production, Arch. Int. Med. **21**:613-620 (May) 1918.

TABLE 2.—Alcohol Checks for 1919-20

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat			Oxygen			Carbon Dioxide			Water			R. Q. Theory 0.667
			Theory, Cal.	Found, Cal.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	
12/5/19	1	12.87	81.45	81.16	—0.3	23.99	23.85	—0.1	21.99	21.62	—1.7	14.86	15.18	+2.2	0.659
89.4	2	12.53	79.30	81.48	+2.7	23.35	23.31	0.0	21.40	21.40	0.0	14.47	14.96	+3.4	0.668
	3	12.63	79.91	79.83	0.0	23.53	22.93	—2.6	21.57	21.23	—1.6	14.58	14.92	+2.3	0.673
	4	12.64	80.00	77.78	—2.8	23.56	23.02	—2.3	21.59	20.77	—0.4	14.60	14.90	+2.1	0.657
Average	...	.....	80.17	80.06	—0.1	23.61	23.28	—1.4	21.64	21.26	—1.3	14.63	14.99	+2.5	0.664
2/26/20	1	11.15	70.54	71.91	+1.9	20.77	19.96	—3.9	19.04	18.54	—2.6	12.87	13.22	+2.7	0.675
89.4	2	10.84	68.58	68.14	—0.6	20.19	21.39	+5.9	18.51	17.74	—4.2	12.52	12.73	+1.7	0.603
	3	11.21	70.95	71.75	+1.2	20.89	20.45	—2.1	19.15	18.65	—2.9	12.95	13.28	+2.5	0.663
Average	...	.....	70.02	70.60	+0.8	20.62	20.60	— 0.1	18.90	18.31	—3.1	12.78	13.08	+2.3	0.646
2/28/20	1	10.98	69.47	69.11	—0.5	20.45	20.30	—0.7	18.75	18.08	—3.5	12.68	13.58	+7.1	0.648
89.4	2	10.67	67.52	68.38	+1.3	19.88	20.14	+1.3	18.22	17.21	—5.5	12.32	13.32	+8.1	0.621
	3	10.31	65.23	66.57	+2.1	19.21	19.02	—1.0	17.61	16.47	—6.5	11.90	12.94	+8.7	0.630
Average	...	.....	67.41	68.02	+0.9	19.85	19.82	—0.2	18.19	17.25	- 5.2	12.30	13.28	+8.0	0.633
3/15/20	1	11.66	73.81	74.30	+0.7	21.73	19.22	—11.5	19.92	19.67	—1.3	13.47	14.07	+4.5	0.745
89.4	2	11.31	71.56	71.29	—0.4	21.07	20.44	— 3.0	19.31	18.92	—2.0	13.06	13.30	+1.8	0.673
	3	11.15	70.56	71.90	+1.9	20.78	21.03	+1.2	19.04	18.74	—1.6	12.88	13.63	+5.8	0.648
	4	11.19	70.80	71.13	+0.5	20.84	20.80	—0.2	19.11	18.54	—3.0	12.92	13.34	+3.3	0.648
Average	...	.....	71.68	72.16	+0.7	21.11	20.37	—3.5	19.35	18.97	—2.0	13.08	13.59	+4.0	0.677
3/18/20	1	11.70	72.96	75.22	+3.1	21.48	21.25	—1.1	19.69	19.47	—1.1	13.49	13.84	+2.6	0.666
3/22/20	1	12.64	78.80	82.69	+4.9	23.20	22.35	—3.7	21.27	20.85	—2.0	14.57	15.11	+3.7	0.678
88.1	2	12.22	76.22	80.18	+5.2	22.44	22.20	—1.1	20.57	20.34	—1.1	14.09	14.60	+3.6	0.666
	3	12.27	76.51	79.60	+4.0	22.53	22.19	—1.5	20.65	20.09	—2.7	14.15	14.66	+3.6	0.659
Average	...	.....	77.18	80.82	+4.7	22.72	22.25	—2.1	20.83	20.43	—1.9	14.27	14.79	+3.6	0.668
5/6/20	1	12.27	76.53	77.41	+1.2	22.53	22.24	—1.3	20.66	20.11	—2.7	14.15	14.64	+3.5	0.658
88.1	2	11.89	74.15	74.88	+1.0	21.83	21.21	—2.8	20.01	19.49	—2.6	13.71	14.29	+4.2	0.668
	3	11.88	74.09	75.64	+2.1	21.82	21.76	—0.3	20.00	19.67	—1.7	13.70	14.29	+4.3	0.658
Average	...	.....	73.92	75.98	+2.8	22.06	21.73	—1.5	20.22	19.76	—2.3	13.85	14.41	+4.0	0.661
Totals.....	.....	.....	1548.94	1570.35	+1.4	456.07	449.06	—1.5	418.06	407.60	—2.5	283.94	298.80	+5.2	0.660

after eating. As a rule the observations were started in the latter part of the third hour or early in the fourth hour.

In the direct calorimetric calculation of the heat lost from or stored in the body, the rectal temperature was used, taking the specific heat only of the body at 0.83. This figure has been found to give fairly accurate results in a considerable series of normal subjects. At best, however, it can be considered as merely an average figure. For different individuals it must vary considerably, depending on the proportions of the various tissues in the body, especially of fat (specific heat = 0.45) and water (specific heat = 1).[19] Moreover, even though the specific heat is not known exactly, it may be considered to remain constant during short periods. The body weight for short periods is likewise a constant. With this in view, a comparison in each hour of the heat production (calculated from the respiratory exchange) with the heat elimination (measured directly) will show that the change in the rectal temperature does not always parallel that of the average body temperature.

The surface area in each case was determined from the height and weight by the "height-weight chart" of Du Bois and Du Bois.[20] In calculating the variations of the metabolism from the average normal, based upon the surface area, the normal heat production per square meter of body surface has been taken from the table given by Aub and Du Bois,[21] which takes into account the effect of age. If the predictions of the normal metabolism for each individual in the series based upon the figures of Aub and Du Bois are compared with the predictions for the same individuals made from Benedict's tables[22] the average difference between the two predictions will be found to be about 3 per cent.

ALCOHOL CHECKS

Interspersed throughout the series were a number of alcohol checks. The first four cases of the series were studied in 1917. The alcohol checks for that period are to be found in Table 1. As the calorimeter had not been in use during the war it was necessary to make quite a number of checks before the apparatus was finally put in good condition. A satisfactory check was first obtained on Dec. 5, 1919, so

19. Rubner, M.: Kalorimetrie, Tigerstedt's Handb. d. physiologische Methoden, Hirzel, Leipzig, 1911, **1**:170, Part. 3.

20. Du Bois, Delafield, and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

21. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

22. Harris, J. A., and Benedict, F. G.: A Biometric Study of the Basal Metabolism in Man, Carnegie Int. Wash., 1919, Pub. 279.

that patients were not studied until after that date. The results of the alcohol checks for 1919-1920 are given in Table 2.

During all of the previous work with the calorimeter a special soda lime was used.[23] This same soda lime was used up to Feb. 12, 1920. At this time a new soda lime, which had been devised for use in submarines, was introduced. This product contained relatively little sodium hydroxid and, consequently, the water formed in the reaction with carbon dioxid was not held in the soda lime but passed off rapidly into the sulphuric acid of the last absorber in the train. The efficiency of this latter absorber was not great enough to handle all of this moisture. The result is seen in examining the alcohol checks for February 26 and 28, and March 15. In these checks the carbon dioxid found was too low, while the results for oxygen consumed and for heat check fairly well. The effect of this error is to give respiratory quotients which are too low. The results for the direct calorimetry are quite satisfactory, and the error in the indirect calorimetry is small, since the indirect calculation is based on the oxygen, for which better checks were obtained.

After March 15, 1920, the Stanley Jordan soda lime was again used, the checks for March 18 and 22 being satisfactory for the purpose of this study.

REPORT OF CASES [24]

CASE 1.—Charles G. *Tuberculosis of pleurae and peritoneum.*

History.—A laborer, 31 years of age, born in the United States, was admitted to the service of Dr. Charles Nammack in Bellevue Hospital April 13, 1917, and discharged unimproved June 3, 1917.

September, 1916, he had pleurisy with effusion on the left side. March 12, 1917, he began to feel pain, localized to a small area in the epigastrium. He had much flatulence. Five days later he noticed that his abdomen was swollen. He had been constipated and the pain had steadily increased in intensity. He had severe night sweats but no cough.

Physical Examination.—Patient was a poorly developed, emaciated negro; height 165 cm.; weight 52.4 kg. The tongue showed a white coat. There were signs of fluid on the right side of the chest to one inch below the spine of the scapula and, on the left, to the angle of the scapula. There was harsh breathing, with many râles above the level of the fluid. The heart was overacting. The rate was rapid, 120 or more, when the patient was in dorsal decubitus. The abdomen was tense and offered a boggy resistance to palpation. There was dulness in both flanks and a distinct fluid wave.

Laboratory Examination.—Urine showed a trace of albumin, hyaline and granular casts. The sputum was examined but no tubercle bacilli were found. Usually his cough was unproductive. The roentgenogram showed pleural effusion on both sides, but no lung involvement.

April 14, in the general ward, the abdomen was tapped and 3,800 c.c. of cloudy, blood-tinged fluid were removed. A guinea-pig, injected with this

23. Made by the Stanley Jordan Company, New York.

24. The first four cases were studied by D. P. Barr in 1917; the remainder by W. S. McCann in 1919-1920.

fluid, died of intercurrent infection April 30, showing no sign of tuberculosis. April 23 the right chest was tapped and 1,500 c.c. of cloudy, straw-colored fluid were removed.

May 7 he was admitted to the metabolism ward. He was observed in the calorimeter May 8, 11 and 14. With temperature varying from 37.8 to 38.1 C., his basal metabolism was 13 per cent. above the average normal. His right chest was tapped a second time May 15 and 400 c.c. of thick, bloody fluid were withdrawn. While in the ward he ran a remittent temperature. The symptoms remained unchanged. He maintained his weight and had an excellent appetite. June 3 he was discharged unimproved.

TABLE 3.—Diet Chart and Nitrogen Balance in Case 1

Name and Date	Food			Food N, Gm.	Urine N, Gm.	Feces N, Gm. (Estimated)	Excreta N, Gm.	N Balance, Gm.	Body Weight, Kg.
	Total Calories	Carbohydrate, Cals.	Fat, Cals.						
Charles G.									
5/ 8/17	2,247	925	981	13.3	12.5	1.3	13.8	—0.5	53.1
5/ 9/17	2,233	967	889	14.7	11.2	1.5	12.7	+2.0	
5/10/17	2,179	908	909	14.1	11.2	1.4	12.6	+1.5	52.5
5/11/17	2,225	860	1,006	14.0	12.5	1.4	13.9	+0.1	
5/12/17	2,668	1,017	1,257	15.4	13.4	1.5	14.9	+0.5	
5/13/17	2,733	1,110	1,229	15.4	13.5	1.5	15.0	+0.4	53.5
5/14/17	1,575	636	686	10.0	9.0	1.0	10.0	0.0	
5/15/17	2,639	1,159	1,082	15.5	13.6	1.6	15.2	+0.3	53.7
5/16/17	2,614	1,057	1,166	15.3	11.9	1.5	13.4	+1.9	
5/17/17	1,580	899	595	3.4	8.3	1.0	9.3	—5.9	53.0
5/18/17	2,637	1,383	1,167	3.4	8.3	1.0	9.3	—5.9	53.2
5/19/17	2,635	1,280	1,268	3.4	4.9	1.0	5.9	—2.5	53.7
5/20/17	2,575	1,269	1,221	3.3	4.5	1.0	5.5	—2.2	52.4
5/21/17	2,548	1,261	1,211	3.0	5.0	1.0	6.0	—3.0	52.7
5/22/17	2,400	1,061	1,255	3.3	5.1	1.0	6.1	—2.8	52.8
5/23/17	2,091	947	1,072	2.8	4.3	1.0	5.3	—2.5	52.2
5/24/17	2,635	1,114	1,136	15.0	8.2	1.5	9.7	+5.3	52.5
5/25/17	2,875	1,482	1,300	3.6	5.9	1.0	6.9	—3.3	52.6
5/26/17	2,973	1,705	1,189	3.1	5.2	1.0	6.2	—3.1	52.6
5/27/17	2,951	1,690	1,185	3.0	4.4	1.0	5.4	—2.4	52.7
5/28/17	2,725	1,421	1,224	3.1	4.8	1.0	5.8	—2.7	52.9
5/29/17	3,167	1,950	1,142	2.9	4.7	1.0	5.7	—2.8	52.1
5/30/17	3,138	1,886	1,178	2.9	4.7	1.0	5.7	—2.8	52.4
5/31/17	3,019	1,826	1,106	3.4	5.0	1.0	6.0	—2.6	52.1
6/ 1/17	2,905	1,570	1,260	2.9	4.9	1.0	5.9	—3.0	

Case 2.—Trellis H. *Tuberculosis of lungs and lymph nodes.*

History.—A waiter, 24 years of age, born in the United States, was admitted to the service of Dr. Robert J. Carlisle May 3, 1917, and discharged unimproved May 22, 1917. The history was not satisfactory because of the very limited intelligence of the patient. In 1913 he had empyema, for which he was treated at the Presbyterian Hospital in Chicago.

April 15 he noticed for the first time a mass beneath the chin on the left side, which grew rapidly. About two weeks later he found that a similar, smaller mass had appeared on the right side. He had had an occasional dry, tickling cough, but no night sweats.

Physical Examination.—Patient was a poorly developed, poorly nourished boy, mentally deficient, height 168 cm., weight 51.6 kg. The teeth showed a marked pyorrhea and were in very bad condition. In the submental region and at the angles of the jaw there were large, hard, semi-elastic, painless masses. The swelling at the angle of the jaw on the right side was hot and showed slight fluctuation. There was a chain of very hard, discrete glands in the right groin; another of similar character in the left axilla.

Lungs: At both apices anteriorly and posteriorly there was dulness to percussion. There was high pitched, almost tubular breathing over the left apex posteriorly and there were a few subcrepitant râles over the right apex.

Laboratory Examination.—The urine was negative. Blood: Leukocytes, 8,200; polymorphonuclears, 69 per cent.; erythrocytes, 4,400,000; hemoglobin, 75 per cent. Wassermann negative. Von Pirquet positive. The roentgenogram showed marked peribronchial infiltration in the left upper lobe between the first and third ribs. The sputum was repeatedly examined, but no tubercle bacilli were found.

May 9: Basal metabolism, with temperature from 40.1 to 40.2 C., was 29 per cent. above the average normal, and with temperature between 39.7 and 40.1 C., it was 43 per cent. above the average normal, due, in part, to coughing.

His condition did not change while in the hospital. His temperature was irregular. May 22 he was transferred to a tuberculosis sanitarium.

Case 3.—Robert W. *Pleurisy with effusion.*

History.—A ship's carpenter, 39 years of age. He was admitted April 23, 1917, and discharged improved on June 2, 1917. He had been in the Navy for eight years. For the past six years he had been on mercantile vessels. In 1900 he had pneumonia, with which he was ill for one month. He had always been a very heavy drinker. He denied venereal disease.

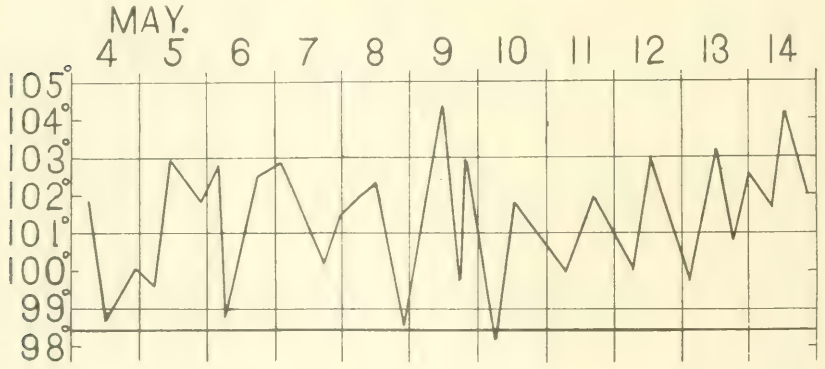

Fig. 1.—Temperature chart of Trellis H.

April 13 he began to feel short of breath, coughed frequently and had some pain in the epigastrium and along the sternum. Coughing or deep breathing increased the pain.

Physical Examination.—Patient was a well developed, rather emaciated man who showed a moderate degree of cyanosis, height 165 cm.; weight 53.4 kg. Lungs: There was absence of fremitus, flatness on percussion, distant voice and distant bronchovesicular breathing over the entire left lung. The right lung was normal. Heart: Was pushed to the right. The right border was 8 cm. to the right of the midsternal line. The left border of dulness merged with flatness of fluid. Coughing was unproductive.

Physical Examination.—One sample of sputum was obtained, but contained no tubercle bacilli. Urine: negative. Blood: Leukocytes, 8,400; polymorphonuclears, 64 per cent.; lymphocytes, 27 per cent. Roentgenogram showed pleurisy with effusion on the left side, but indicated no lung involvement.

April 24, 1,400 c.c. of straw-colored fluid were removed from the left chest. No tubercle bacilli were found. April 26, after 2,000 c.c. had been withdrawn, there were still signs of fluid. May 3 the chest was again filled with fluid, 3,500 c.c. of which were withdrawn. May 15 the level of the fluid was from the middle of the scapula behind to the third rib in front. May 17 1,400 c.c. were withdrawn, after which the level of fluid was at the eighth rib in the midscapular line. May 25 at 8:15 a. m. he had a chill, the cause of which was

not apparent. On the same day, from 10:30 a. m. to 2:30 p. m., he was observed in the calorimeter, temperature falling from 40.10 to 39.36 C., metabolism 29 per cent. above the average normal.

He was in the calorimeter May 28 while the temperature was normal. In the course of this observation, however, he was seized with abdominal pain. During the rest of the day he had a diarrhea, and passed fourteen stools which contained much blood and mucus. This continued until May 31. Careful examination of the centrifugalized stools revealed no tubercle bacilli. June 2 he was discharged from the hospital. His temperature was normal. The signs of fluid did not change after May 17.

Case 4.—George P. *Acute miliary tuberculosis; tuberculoma of left eye.*

History.—A laborer, 18 years of age, born in Greece, was admitted April 23, 1917, and discharged June 12, 1917. He came to this country from Greece in January, 1917. He had never had any serious illness.

The latter part of March, 1917, he lost his appetite, felt feverish, and had several night sweats. A few days later he found that he could not see with his left eye. He had coughed continually since the onset of the trouble, and for a month had sharp, stabbing pain in the left side of the chest. Since he came to this country he had lost twenty-five pounds in weight, dropping from 154 to 129 pounds.

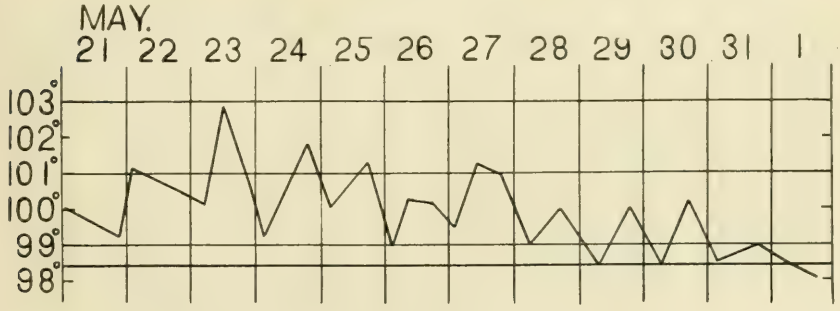

Fig. 2.—Temperature chart of Robert W.

Physical Examination.—Patient was a well developed, moderately emaciated boy, height 172 cm., weight 58.5 kg. His face showed a high color and his vasomotor system was very unstable. The eyes were normal externally. The retina of the right eye was normal. In the left retina there was a tumor, white in color, above and to the temporal side of the optic disk, about two disks in width, three disks in length. It was elevated six diopters above the surrounding retina. There was a small hemorrhage into the retina on the temporal side of the tumor. Lungs: There was a dulness to percussion and prolonged, high pitched, bronchial breathing at the right apex posteriorly. Anteriorly there were many constant, fine râles. At the left base there were many coarse, leathery friction râles. The cervical, axillary and inguinal lymph nodes were palpable.

On later examination, April 22, the tumor in the left retina was found to be elevated eleven diopters and to have spread to involve the optic disk.

Laboratory Examination.—Urine: negative. Blood: Leukocytes, 7,000; polymorphonuclears, 70 per cent.; erythrocytes, 3,600,000. Tuberculosis fixation test was positive. Questionable tubercle bacilli were found once in the sputum. The roentgenogram showed a diffuse miliary tuberculosis with a cavity at the right apex.

May 24, he was observed in the calorimeter; temperature varied from 37.5 to 37.8 C.; basal metabolism, 11 per cent. above the average normal.

The cough and pain in the chest continued and were very troublesome. With the exception of the rapid growth of the tuberculoma in the left eye, his condition changed very little after admission to the hospital. He was sent to a tuberculosis sanitarium June 12.

TABLE 4.—Diet Chart and Nitrogen Balance in Case 4

Name and Date	Total Food, Cals.	Carbohydrate, Gm.	Fat, Gm.	Food N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Weight, Kg.
George P.							
5/24/17	1,800	208	72	10.6	10.0	+0.6	58.6
5/25/17	2,500	241	120	15.1	11.8	+3.3	58.6
5/26/17	2,530	236	125	15.6	13.4	+2.2	58.1
5/27/17	2,530	242	122	15.8	17.4	—1.6	58.5
5/28/17	2,580	283	110	15.0	15.1	—0.1	
5/29/17	2,930	420	122	2.9	10.2	—7.3	58.4
5/30/17	3,140	458	127	3.0	6.4	—3.4	
5/31/17	3,040	449	119	3.5	5.5	—2.0	59.2
6/ 1/17	2,960	395	136	3.1	5.1	—2.0	
6/ 2/17	2,380	283	123	2.9	4.2	—1.3	58.1
6/ 3/17	2,600	336	123	3.1	5.0	—1.9	
6/ 4/17	2,700	346	128	3.4	4.8	—1.4	58.1

* Fecal nitrogen estimated.

Case 5.—Spencer C. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—A negro, aged 46 years, was admitted Dec. 8, 1919, complaining of shortness of breath, weakness and cough. One brother had died of tuberculosis. The patient's early life had been spent under poor conditions, but his health had been good up to 1916 when he was discharged from the army. Since then his occupation had been that of janitor. During the last two years he had continually "felt below par," progressively losing weight and strength. During this time he had a chronic cough which was worse at night and frequently kept him from sleeping. The cough became productive of a tenacious, greenish sputum in which he had never noted the presence of blood. During the year before admission, the wasting progressed rapidly, so that he was sixty-five pounds below his best weight (163 pounds). He had occasional night sweats. In the past few months he had noted increasing shortness of breath, at first only on exertion, but later while lying in bed. His cough had become so severe as to induce vomiting. One month before admission he had dull pains all over the chest, but these had disappeared. His appetite was whimsical. Bowels were constipated.

Physical Examination.—Patient was a fairly well developed, emaciated negro, lying flat in bed but showing considerable dyspnea, height 169 cm., weight 44.4 kg. Lips showed some cyanosis. Facies showed exhaustion and lethargy. Eyes were very prominent, with considerable bulging of the periocular tissues. The few remaining teeth were carious. The tonsils were markedly enlarged and cryptic. On both sides of the neck there were numerous, enlarged lymph nodes about the size of a bean. Thorax: showed retractions above and below both clavicles. The expansion was poor, but more limited on the right side. Lungs: showed impaired resonance over the entire chest, more marked on the right side. On auscultation bronchial breathing was heard over both upper lobes, with many medium and coarse râles heard over the entire chest. Near the inner end of the spine of the right scapula posttussive suction was heard. Heart: not enlarged. The first sound was of poor quality, the pulmonary second sound was accentuated. Rhythm was regular, but the rate was very rapid. Arteries: thickened but not tortuous.

Blood Pressure: Systolic, 115 mm.; diastolic, 65 mm. Abdominal findings: negative. Lymph nodes: enlarged in neck, axillae, inguinal and epitrochlear regions. Genitalia: normal. Fingers and toes: showed marked clubbing. There was slight edema of the ankles. Reflexes: Achilles and patellar reflexes not obtained.

Laboratory Examination.—The sputum showed numerous tubercle bacilli. Urine: normal, except for low specific gravity. Roentgenogram of chest showed diffuse peribronchial infiltration of the entire right lung, with numerous small cavity formations at the right apex. Numerous foci of peribronchial infiltration scattered irregularly throughout the central portion of the left lung. The temperature course is shown in Figure 3.

The patient was observed in the calorimeter December 10, the basal metabolism being 12 per cent. above the average normal for his surface area during a period of normal temperature.

Patient left hospital two days later and subsequent history is unknown.

Case 6.—Edith B. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—Colored female, aged 20 years, admitted Dec. 12, 1919, complaining of pain in the left side of chest, cough and weakness. One aunt died of

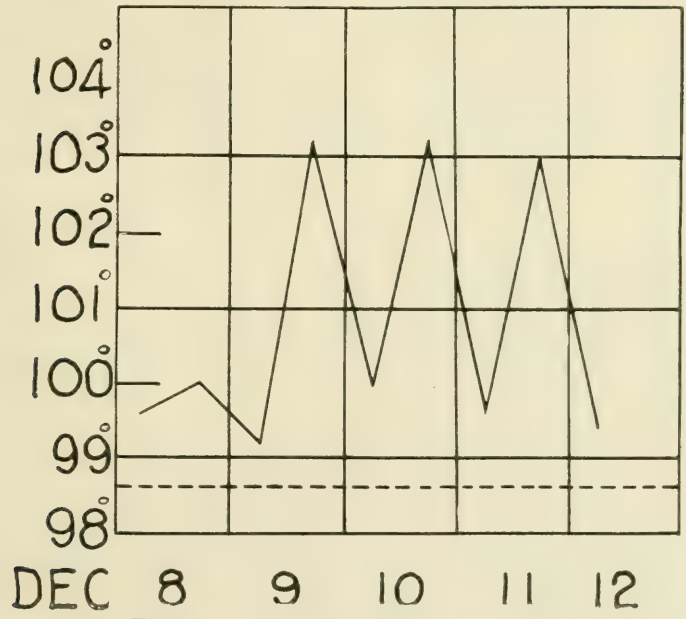

Fig. 3.—Temperature chart of Spencer C.

tuberculosis. Her mother had a disease of the spine with partial paralysis of one leg. The patient had been married eighteen months but had had no pregnancies. In childhood she had whooping cough and measles. In 1916 she had pneumonia. Otherwise her health had been good up to the onset of the present illness. Her normal weight was 135 pounds.

Early in September, 1919, patient became very weak and dizzy about 4 p. m., and at this time she felt chilly. Soon after this she developed a troublesome cough which was much worse at night. She expectorated a moderate amount of mucoid sputum in which no blood was noticed. At this time she was engaged in nursing an aunt who died one month later of consumption. A little later she began to have a great deal of pain in the left side of the chest on coughing and on deep breathing. These symptoms continued to grow worse until she was confined to bed most of the day. Her appetite was very poor. She lost weight, from 135 to 109 pounds. She had "hot fevers" at night, followed by sweats. She was admitted to the service of Dr. James Alexander Miller, through whose kindness she was transferred for study.

Physical Examination.—The patient was a young negro woman, 178 cm. tall, weighing 44.6 kg., alert and intelligent, lying on her side in bed, breathing rapidly and coughing occasionally. Mucous membranes were pale and not cyanotic. Thorax: well formed, but with moderate retractions above and below clavicles, most marked on the left side, involving the second and third interspaces. The expansion of the right side of the chest was fairly free, but there was marked limitation of motion of the left side. Lungs: Percussion note was resonant at both bases, but there was no excursion at the left, while at the right base there was an excursion of 5 cm. Both apices were dull both front and back, more marked on the left. There was diminution of the voice and breath sounds at the left base behind, and over the dull areas the breathing was bronchovesicular or bronchial in character, with many fine râles. Heart: Apex impulse could not be located. The cardiac dulness extended 12 cm. to the left in the fifth intercostal space, but the right border could not be sharply located. Rate rapid; rhythm regular. No murmurs heard. Pulse: rapid and of low tension. Arteries: normal. Abdomen: negative. Genitalia: not examined. Extremities: normal. Reflexes: normal. Epitrochlear lymph nodes: enlarged.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine: normal. Roentgenogram of chest showed infiltration, fibrosis and cavitation of the middle portion of the right lung and the entire left lung with the exception of a small portion of the left base. Cavity formation was located in the upper

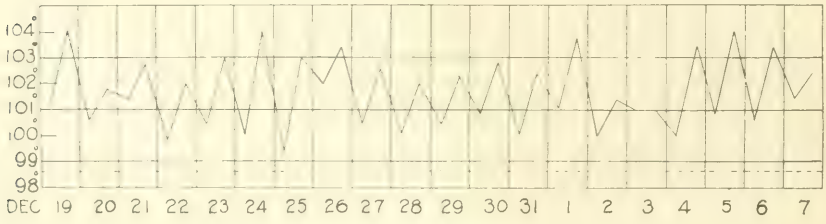

Fig. 4.—Temperature chart of Edith B.

portion of the middle lobe, but there were also numerous small cavities in the left lung. There were many pleuropericardial adhesions, with marked distortion of the cardiac outline. Compensatory emphysema in the right lung and fibrosis in the left lung.

Observations were made in the calorimeter December 7 and 19 and January 6. The first observation made at normal temperature showed no elevation of the basal metabolism. Subsequent observations during high fever, with coughing, raised the metabolism from 18 to 20 per cent. above the average normal and still further increases were due to restlessness during the third observation. The mechanism of temperature regulation in this case is shown graphically in Figure 14.

Case 7.—Harry G. *Pulmonary tuberculosis, extensive bilateral infiltration.*

History.—A fountain-pen maker, 18 years of age, was admitted Jan. 2, 1920. complaining of cough, weakness and night sweats. He had measles in childhood, but was well and active, though rather weak as a boy. At the age of 16 he went to work in a fountain-pen factory, where the work was confining and the atmosphere full of dust. His appetite was poor, bowels constipated, but he had no respiratory symptoms until November, 1919.

At that time he caught cold and began to have a racking cough with a moderate amount of viscid sputum. The cough reached its maximum intensity one month before admission, after which it was less troublesome. It was most severe at night, when it sometimes produced vomiting. He had night sweats

before entering the hospital, but none during his stay. Two weeks before admission he coughed up about one teaspoonful of bright blood. He had become very constipated. He had no urinary symptoms. His greatest weight was 123 pounds; admission weight was 109 pounds. He felt loss of strength very much.

Physical Examination.—Patient was a pale, poorly developed, poorly nourished boy of 18 years, height 163 cm., weight 42.7 kg. There were small but distinctly palpable nodes on both sides of the neck. Thorax was carinate. There was retraction above and below both clavicles, more marked on the left side. The entire left chest showed retraction and marked limitation of expansion. Lungs: Both upper lobes were dull on percussion, the left to the second intercostal space in front and to the angle of the scapula behind; the right was dull only above the clavicle in front and to the spine of the scapula behind. Over these dull areas the breath sounds were bronchial in quality, with many medium sized and fine râles. No excursion of the left base was found, while the maximum excursion of the right base was 2 cm. At the left base there was slight dulness, bronchovesicular breath sounds and many moist râles, front and back. Heart not enlarged nor displaced. There were no murmurs. The rate was quite rapid, but the rhythm was regular. Pulse was rapid and soft. Blood pressure: Systolic 120 mm.; diastolic 80 mm.

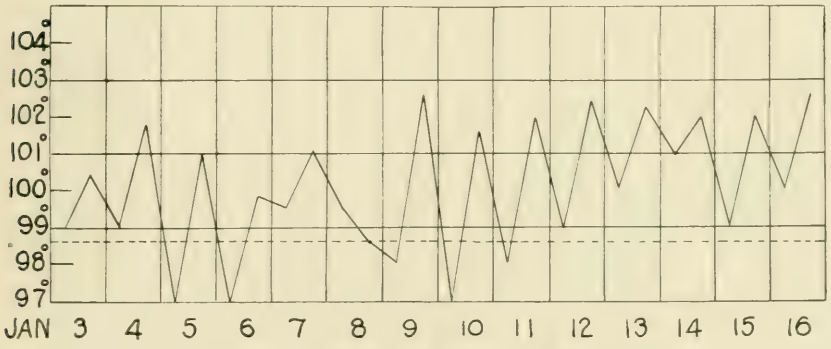

Fig. 5.—Temperature chart of Harry G.

Further examination negative. Urine was normal. Sputum showed numerous tubercle bacilli. Fluoroscopy showed a very diffuse parenchymatous infiltration of both upper lobes, particularly of the left side, with a small antrum beneath the left pole (Dr. J. A. Miller).

One observation was made in the calorimeter January 13. The temperature fell from 39.20 to 38.94 C., pulse 120. The metabolism was 21 per cent. above the average normal, but the conditions were not basal on account of restlessness.

Case 8.—Joseph D. *Pulmonary tuberculosis, infiltration of both upper lobes and left base.*

History.—A machinist, aged 33 years, was admitted Dec. 3, 1919, complaining of pain in the left side of the chest and cough. His father, mother and one brother died of pneumonia and one uncle died of "lung trouble." In childhood he had dysentery, mumps, whooping cough, "chills and fever." In 1915 he was treated for "lung trouble" in a hospital. He had a bad cough at that time. While under treatment he worked for one year. In April, 1919, he was in Bellevue Hospital on account of pleurisy and cough. Following this he had a chronic cough and occasionally night sweats. He was very short of breath on exertion and had palpitation but no edema. His appetite was good, bowels regular. He urinated three to four times during the night. He had gonorrhea fifteen years ago. His best weight was 135 pounds.

Nov. 25, 1919, while digging a trench, he felt a sudden, sharp pain in the left side of the chest and across the back. He stopped work but did not go to bed. Pain and cough increased daily so that he entered the hospital December 3. At that time the physical findings, confirmed by the roentgen ray, led to a diagnosis of bilateral apical tuberculosis. The temperature range was from 97.4 to 100 F. Leukocytes, 14,000, with polymorphonulcears 65 per cent.; lymphocytes, 23 per cent.; large mononuclears, 10 per cent.; eosinophils, 1 per cent. Hemoglobin, 73 per cent. Urine was normal.

He was allowed to leave the hospital on pass, but did not return. He was readmitted Jan. 14, 1920, with a temperature of 102 F., having had severe chills.

Physical Examination.—A well developed, fairly well nourished man, height 177 cm., weight 59 kg., face flushed, eyes bright, respirations rapid but not labored. Chest: Retraction of both supraclavicular and infraclavicular fossae. Expansion limited most markedly on the right side. Lungs: Both apices were dull from the second intercostal space in front to the spine of the scapula behind and there was dulness at the left base behind. Breath sounds at both apices were tubular, with crepitant and moist râles. In the left chest in front there was a coarse friction rub between the fourth and seventh intercostal spaces. At the left base behind many coarse râles were heard. Heart was not enlarged; rate 80; rhythm regular; no murmurs. Pulse was full and soft, artery not thickened. Further examination was negative.

The patient improved rapidly though he had a moderate, irregular fever for about nine days. January 15 he complained of huskiness of the voice and pain in the larynx on swallowing. Examination showed a thickening of the arytenoids and of the anterior commissure. The cords were thickened and lacked the normal luster but approximated throughout.

Laboratory Examination.—Sputum showed no tubercle bacilli. The roentgen ray showed a patch of peribronchial infiltration in the peripheral portion of the right apex. There was fibrosis of the left apex, emphysema of both lungs, more on the right. There was production of fibrous tissue in the lower lobe of the left lung, but no peribronchial infiltration. Adhesions at the left base.

Diagnosis.—Early second stage tuberculosis, right apex; fibroid tuberculosis, left apex; interstitial inflammation of the left lower lobe; pleural thickening of the right upper lobe; deviation of the heart to the right, axis almost vertical.

The last day of fever was January 16. He was put in the calorimeter on the seventeenth, at which time his basal metabolism was found to be .90 per cent. of the average normal in one hour in which he was very quiet.

Case 9.—Michael C. *Pulmonary tuberculosis with cavitation, laryngeal tuberculosis.*

History.—A furrier, aged 33 years, complained of hoarseness and shortness of breath. He was in perfect health up to January, 1919, when he engaged in a drinking bout with some friends. He sang very loudly and on the following day he was quite hoarse. Soon a cough developed with some expectoration. No medicine gave any relief, his cough and hoarseness grew worse, he began to have night sweats and to lose weight and strength. He remained at work, however, until August, 1919. At this time he became very short of breath and felt great oppression of the chest. His cough was more and more productive, but hemoptysis occurred on only one occasion and then in very small amount. He spent November and December in Colorado, where he improved somewhat. Two weeks before admission he returned to New York. He caught cold and had a recurrence of his worst symptoms. He developed complete aphonia. His best weight was 130 pounds; admission weight was 110 pounds.

Physical Examination.—Fairly well developed but emaciated man, height 179 cm., weight 50 kg., lying flat in bed, breathing rapidly, extremely weak and ill. Laryngeal examination was difficult, but showed marked congestion of epiglottis, arytenoids and vocal cords and laryngeal walls. There were a few enlarged lymph nodes in the neck on both sides. Thorax was well formed,

but there were retractions above and below both clavicles. Expansion was limited on both sides, but more so on the right. Lungs: Both apices dull to percussion, right front dull to the fifth rib and behind to the angle of the scapula. The left apex was dull from the second rib to the middle of the scapula behind. Over the dull areas the breathing was in general broncho-vesicular, with many fine and medium moist râles. Over the third intercostal space in the mid-clavicular line the breathing was amphoric in character. Further examination was negative.

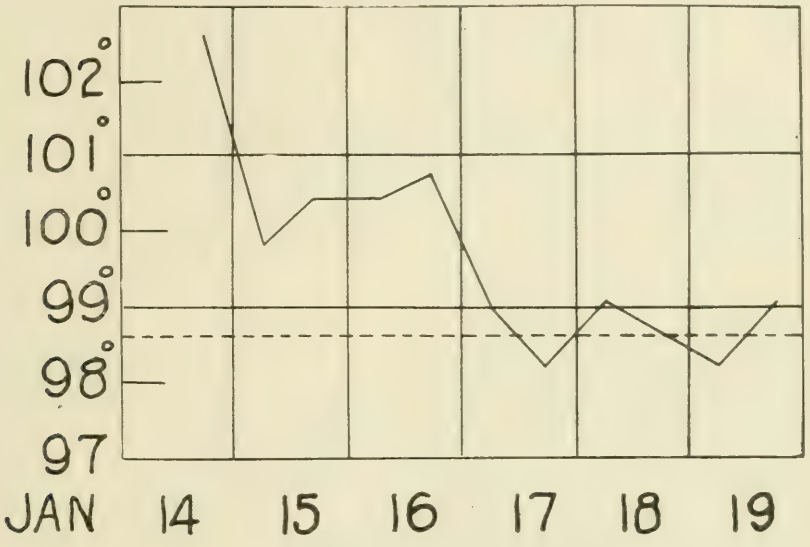

Fig. 6.—Temperature chart of Joseph D.

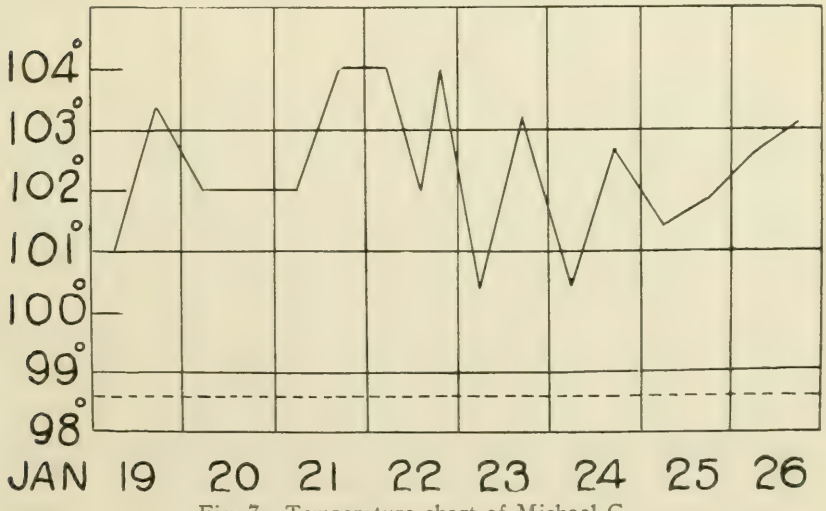

Fig. 7.—Temperature chart of Michael C.

Pulse ranged from 86 to 128 and respirations from 22 to 28. Sputum was full of tubercle bacilli. Urine was normal.

The patient was observed in the calorimeter Jan. 22, 1920. With the rectal temperature falling from 39.8 to 39.2 C. and pulse 120, the metabolism was 31 per cent. the first hour and 24 per cent. the second hour above the average normal; the conditions were not basal as the patient coughed incessantly. The subsequent history is unknown.

Case 10.—Anna H. *Bronchopneumonia; phthisis.*

History.—Sewing machine girl, aged 17 years, was admitted Jan. 25, 1920, complaining of pain in the chest and cough. She had worked two years in the factory, during which time her weight had dropped from 122 pounds to 113 pounds. She was well up to the onset of the present illness, which began Nov. 25, 1919, with a bad cold. The cold did not improve, but she remained at work until Jan. 11, 1920, when her illness became acute, with severe cough and pains in the chest. After remaining in bed for two days she attempted to return to work. She became worse rapidly, coughed constantly and had night sweats. Her weight dropped from 113 to 90 pounds.

Physical Examination.—On admission, January 25, the pharynx was congested, tongue coated, heart normal. Lungs showed no dulness, but numerous, squeaking râles were heard on both sides in back. Temperature, 103 F.; pulse, 100.

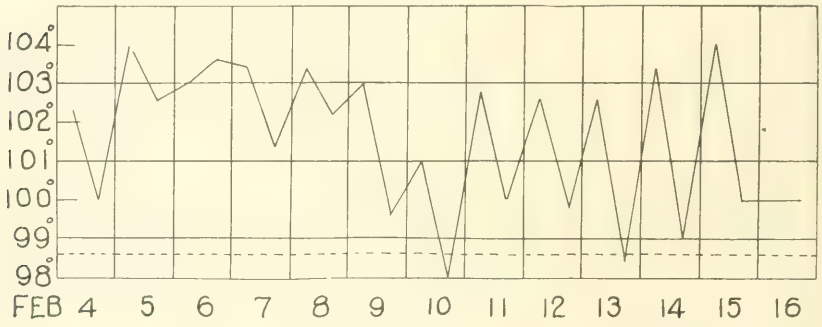

Fig. 8.—Temperature chart of Anna H.

Tentative Diagnosis.—Acute bronchitis.

January 28 numerous tubercle bacilli were found in the sputum. On the following day a note was made: "Thorax symmetrical and well developed. Respiratory excursion is slightly restricted. There are no retractions or bony prominences. There is a widespread process extending through all lobes of both lungs, but most advanced at the bases, characterized by bronchovesicular breathing, and many fine, medium and large moist râles. At both bases posteriorly there is dulness, most marked at the left. At the apex of the heart there is a localized systolic murmur. Over the base of the heart there is a longer, rough murmur heard in systole."

Laboratory Examination.—Urine examinations were all normal. Blood: Feb. 4: Leukocytes, 10,000; polymorphonuclears, 70 per cent.; transitionals, 2 per cent.; lymphocytes, 25 per cent.; eosinophils, 3 per cent. Hemoglobin, 60 per cent.

She was studied in the calorimeter February 5. The temperature rose from 39.38 to 39.64 C.; pulse 132. The metabolism was 21 per cent. above the average normal, but was not basal, as the patient was coughing throughout the observation.

February 7 the physical examination was as follows: "A normally developed girl of 17, past puberty, very emaciated and pale, height 165 cm., weight 41 kg. There is a bright flush over the left malar region; eyes are bright; breathing very rapid but not labored. Thorax shows limitation of expansion of the left

side. There are retractions above the clavicles, and on the left side in the first and second interspaces and at the left base and axilla. Lungs are dull at both apices, and the left lung is dull throughout. The right base is resonant below the angle of the scapula. Over the dull area there is an increase in vocal and tactile fremitus, tubular breathing at the apices and bronchovesicular breathing at the left base. Over the whole chest fine, medium and coarse moist râles are heard. Heart is normal. Pulse rapid, 120, regular, and of very low tension. Abdomen is somewhat distended, but otherwise normal." Further examination was negative.

February 20 the signs of consolidation were intensified. Numerous crackling râles and in many places creaking friction rubs were heard.

The patient died two days later. A necropsy was not permitted.

Case 11.—John H. *Pulmonary tuberculosis.*

History.—A chauffeur, aged 25 years, was admitted complaining of pain in the chest, headache and chills. He was well and strong up to the time of his enlistment in the British Army, Tank Service, in 1916. He served nine months at the front and remained well until he was gassed with chlorin. He was sick for three or four months with cough and afternoon fever, but was finally returned to duty. He remained well and was discharged physically fit. He was able to do all sorts of work up to the end of November, 1919, when he

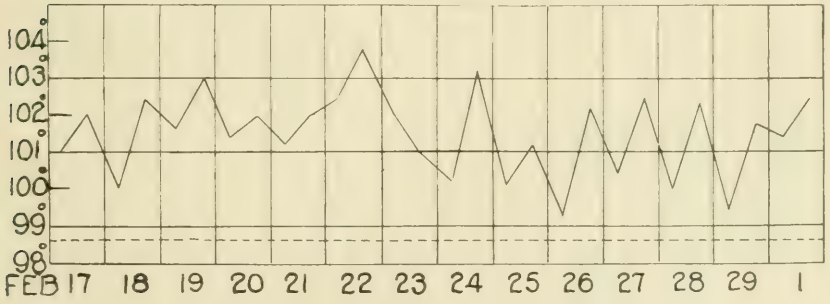

Fig. 9.—Temperature chart of John H.

was taken sick with pneumonia and treated in the Metropolitan Hospital for four weeks. He had been out of the hospital only three weeks when he was again taken sick and admitted to Bellevue Jan. 24, 1920. Three days before admission patient had a severe cough and soreness in the chest. He went to bed and stayed there until the following day. A doctor gave him some whisky. He took it and the next day was admitted in an intoxicated condition. Later he said his best weight was 142 pounds and that he had maintained this up to November. Present weight, 100 pounds.

Physical Examination.—Height, 175 cm., weight 45 kg. Well developed, pale, emaciated young man. Lips somewhat cyanotic and parched. Chest: Well formed with deep supraclavicular fossae. Expansion was fairly good, but more limited on the right side. Lungs: Left apex was dull from the second rib in front to midscapula behind, with bronchovesicular breathing and many fine râles. Left base was resonant except in midaxilla, where there was slight dulness and a creaking rub was heard. The right lung was dull throughout, most marked at the apex, where the breath sounds were tubular and accompanied by fine râles. At the right base the breathing was bronchovesicular, with many medium and fine râles. Heart was normal in size and position; no murmurs. Rhythm was regular. Pulse was soft and rapid. Blood pressure: Systolic 100; diastolic 60. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte counts, January 26. 10,500; February 6, 13,600; polymorphonuclears, 64 per cent.; transitionals, 18 per cent.; lymphocytes, 4 per cent.; large mononuclears, 13 per cent.; eosinophils, 1 per cent. Roentgenogram of chest, February 9, showed diminished illumination over the upper halves of both pulmonic fields. There was considerable increase in the size, number and density of the pulmonic markings throughout this area. These markings were confluent. There was considerable increase in density of both hilus shadows. The costophrenic sinuses were clear. The diaphragmatic outlines were normal. The heart shadow was slightly displaced to the left. Infiltration of upper halves of both lungs.

Diagnosis.—Tuberculosis.

He was studied in the calorimeter February 10. With a normal temperature his basal metabolism was 15 per cent. above the average normal. February 12, the specific dynamic effect of a meat meal was studied (Fig. 15). This meal

TABLE 5.—Diet Chart and Nitrogen Balance in Case 11

Name and Date	Food			Food N, Gm.	Urine N, Gm.	Feces N, Gm.	Excreta N, Gm.	N Balance, Gm.	Body Weight, Kg.
	Total Calories	Carbohydrate, Gm.	Fat, Gm.						
John H.									
4/17/20	1,650	147	83	10.7	9.0	1.1	10.1	+0.6	44.6
4/18/20	1,977	185	92	14.2	....	1.4			
4/19/20	1,830	194	73	13.8	9.0	1.4	11.4	+2.4	44.3
4/20/20	.....	...	...	....	6.8	...	....	.....	44.7
4/21/20	.....	...	...	....	10.8				
4/23/20	1,890	156	95	14.5	....	1.5	....	.....	43.8
4/27/20	1,848	152	93	14.1	14.5	1.4	15.9	—1.8	
4/28/20	1,848	152	93	14.1	17.6	1.4	19.0	—4.9	44.0
4/29/20	1,848	152	93	14.1	13.7	1.4	15.1	—1.0	44.2
4/30/20	1,964	173	95	14.4	12.3	1.4	13.7	—0.7	43.9
5/ 1/20	1,964	173	95	14.4	11.6	1.4	13.0	+1.4	43.8
5/ 2/20	2,055	180	100	15.0	11.6	1.5	13.1	+1.9	
5/ 3/20	2,123	185	104	15.7	13.9	1.6	15.5	+0.2	44.3
5/ 4/20	1,734	169	92	7.1	7.6	2.1*	9.8	—2.6	
5/ 5/20	1,739	169	93	7.1	8.8	2.1*	10.9	—3.8	44.7
5/ 6/20	1,739	169	93	7.1	5.7	2.1*	7.8	—0.7	44.7
5/ 7/20	1,737	169	92	7.1	6.4	2.1*	8.5	—1.4	
5/ 8/20	1,737	169	92	7.1	3.8	2.1*	6.9	+0.2	44.7
5/ 9/20	1,737	169	92	7.1	5.6	2.1*	7.7	—0.6	
5/10/20	1,737	169	92	7.1	5.4	2.1*	7.5	—0.4	44.9
5/11/20	2,975	188	121	3.2	5.4	1.0	6.4	—3.2	44.8
5/12/20	2,955	183	121	3.3	4.6	1.0	5.6	—2.3	44.5
5/13/20	1,914	181	118	3.0	3.7	1.0	4.7	—1.7	44.0
5/14/20	1,914	181	118	3.0	3.1	1.0	4.1	—1.1	44.3
5/15/20	1,915	181	118	3.0	....	...	....	.....	44.2

* Analysis made. Remaining fecal nitrogen estimated.

consisted of 350 gm. of lean beef and 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 69.3 calories per hour, his metabolism rose in successive hours after the meal to 77.0, 82.4 and 86.8 calories per hour, respectively. This corresponds closely with the results obtained with normal subjects.

Considerable improvement in the patient's condition occurred, his appetite was better. He still had considerable pain in the left chest.

March 1 his metabolism was 17 per cent. above the average normal, temperature betwen 38.68 and 38.71 C., very quiet.

During the month of March marked improvement continued. The temperature range gradually became smaller and lower. His cough almost ceased. His appetite was good and during this time he was given the ordinary soft, special diet of the hospital, not measured. The total caloric value of this diet is not high. He remained at the same weight, 100 pounds, with very slight variations.

His basal metabolism was again determined April 14; rectal temperature from 37.8 to 37.4 C. His metabolism was 5 per cent. above the average normal. From this his daily basal heat production was estimated at 1,512 calories. This was done as a preliminary to complete dietary control in the metabolism ward. The temperature and graphic record of this study are given in Figure 18. The observed data are given in Table 5. The stools for the different periods were marked off with carmine and saved for analysis, the total nitrogen for the period was determined, and the daily average added to the urine nitrogen figure. The study was made to determine the minimum level at which nitrogen balance could be attained and the minimum to which the protein metabolism could be reduced as a means of estimating the toxic destruction of protein.

Case 12.—William H. *Pulmonary tuberculosis, tuberculosis of hip joint.*

History.—A laborer, aged 31 years, was admitted in February, 1920, complaining of pain in the chest, cough, loss of weight and weakness. At the age of 2 he had whooping cough and later measles. When 3 years old he had hip disease, for which he was treated at the Postgraduate Hospital. He wore a brace until the age of 13. During this period his health was good. His growth was normal. He had always done hard manual labor outdoors until shortly before the present illness. Late in the fall of 1919 he worked in a factory

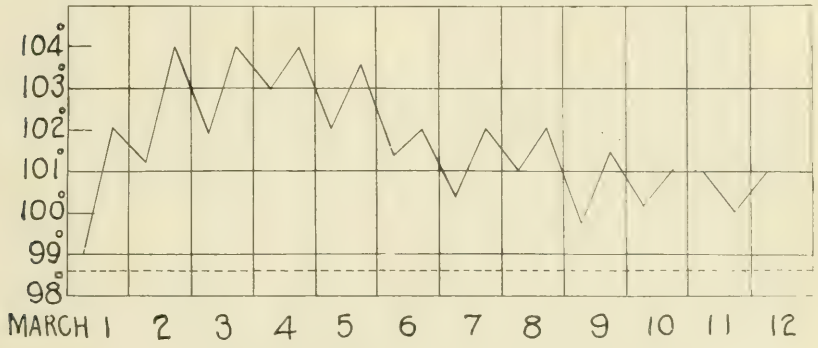

Fig. 10.—Temperature chart of Wm. H.

where he was confined in a dusty room. He felt wretched during his stay in this position and gave it up. He then worked on the city streets shoveling snow. February 7 he became very wet and was exposed all day. He felt a sudden, sharp pain in the left chest and back. In the Bellevue Dispensary tubercle bacilli were found in the sputum and, therefore, he was admitted to the hospital. During the week prior to admission he had night sweats, severe cough, with abundant sputum in which no blood was noted. His best weight was 135 pounds, but just before the onset of illness it was 130 pounds. Weight while in the hospital was 110 pounds.

Physical Examination.—Height 165 cm., weight 49.7 kg. Patient was a fairly well nourished young man of medium size who looked acutely ill. Thorax: Slight asymmetry due to a scoliosis. Respiratory movements fairly free and symmetrical. There were no retractions. Lungs: Apices were dull on both sides above and just below the clavicles. Behind, the dulness, which was most marked at the extreme apex, shaded into normal resonance about the level of the sixth dorsal spine. Over the apices the breath sounds were broncho-vesicular, with many fine râles. Between the scapula many coarse moist râles and sibilants were heard. Elsewhere the breath sounds were normal. Heart: Of normal size and position. No adventitious sounds were heard. The rate was rapid, rhythm regular. Pulse rapid and soft. Blood pressure: Systolic, 105 mm.; diastolic, 85 mm. There was ankylosis of the left hip, with

complete limitation of motion. The muscles of the left thigh and calf were atrophied. The left leg was two inches shorter than the right. There were no other abnormalities.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte count, March 3, 10,400; hemoglobin, 90 per cent. March 8: Wassermann reaction negative. Roentgen-ray report showed pulmonic fields of equal size. There was diminution of illumination over the upper half of the left pulmonic field. The apices were clear. There was considerable increase in the hilum shadows, with calcific foci on the right. The pulmonic markings were increased in size, number and density over the upper half of the left pulmonic field, with agglutination. Over the right pulmonic field there was increase in the size, number and density of the pulmonic markings, with confluence. There was an irregularity in the outline of the right diaphragm. The costophrenic sinuses were clear. The heart was large, generally rounded in outline and median in position.

March 24: Vital capacity equaled 2,795 c.c. The normal for the present surface area, according to the calculations of West, is $1.53 \times 2{,}500 = 3{,}825$ c.c., but the normal surface area for health is 1.66 square meters, hence the normal vital capacity would be 4,150 c.c.

March 2 the metabolism was 18 per cent. above the average normal when his temperature was 38.58 C. and the patient was very quiet. At the same temperature in the next hour the heat production was raised 5 per cent. more by coughing.

March 10 the basal metabolism was 9 per cent. above the average normal when the rectal temperature was 38.0 C.

The specific dynamic action of a protein meal was studied. The meal consisted of 350 gm. meat with 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 65.6 calories per hour, the metabolism rose after the meal to 68.7, 73.9 and 86.1 calories per hour in successive hours. This corresponds closely with the behavior of the normals studied (Fig. 15).

Case 13.—John S. *Pulmonary tuberculosis, mitral stenosis, and regurgitation, compensated.*

History.—A machinist, aged 28 years, was admitted complaining of a feeling of fatigue and of swelling of the feet and ankles. He had no illness in childhood except occasional sore throat. At the age of 20 he had mumps. In 1913 he had typhoid fever. In 1919 he had two attacks of acute rheumatic fever. He had gonorrhea three times. He was in quite good health until the spring of 1919, when he had a severe cold, which persisted. He had a dry, hacking cough, which grew much worse in the course of several weeks. He lost appetite and began to have fever in the afternoon, with great weakness and prostration. He remained at work even when his temperature was high. Sputum examination by the board of health showed tubercle bacilli. At this time his afternoon temperature was 103 F. His weight dropped from 160 to 154 pounds. He was sent to a hospital for tuberculosis and later transferred to Otisville. He improved, became afebrile, and regained weight up to 160 pounds. While there he developed acute rheumatic fever after lying on the wet grass when overheated from work. He soon recovered, but had another attack in August, 1919. Following the second attack he had edema of the ankles while at work. For the past year he had to urinate three or four times during each night. Maximum weight in 1913 was 168 pounds; weight before illness in 1919 was 160 pounds; weight while in hospital, 148 pounds.

Feb. 5, 1920, his feet began to swell and he felt very tired. This continued, causing him to stop work February 10. He was admitted to Bellevue February 12, with a fever of 104 F., falling to normal in the course of forty-eight hours, and then fluctuating between 99 and 100 F. He had a mild cardiac decompensation from which he rapidly recovered, though he continued to have fever from a reactivation of his tuberculosis.

Physical Examination.—Patient was a well developed man, 191 cm. in height, weighing 62.3 kg. Thorax well formed, supraclavicular fossae deep, but

with greater retraction on the left. There was limitation of expansion of the left chest. Lungs were dull on percussion of both upper lobes, the left upper from the fourth rib in front to the angle of the scapula behind, the right from the third rib in front to the midscapula. Expiration was prolonged and high pitched, with many medium and fine râles. Heart: Apex impulse in the fifth intercostal space was 12 cm. to the left of midline. Dulness extended to the left 13 cm. in the fifth space and to the right 6 cm. in the fourth intercostal space. There was a suggestion of a thrill over the precordium. There was a presystolic murmur of rough, crescendo quality at the apex, and also a systolic murmur heard at the apex, in the axilla and to the right of the sternum in the fourth space. The second pulmonic sound was accentuated. The rate was

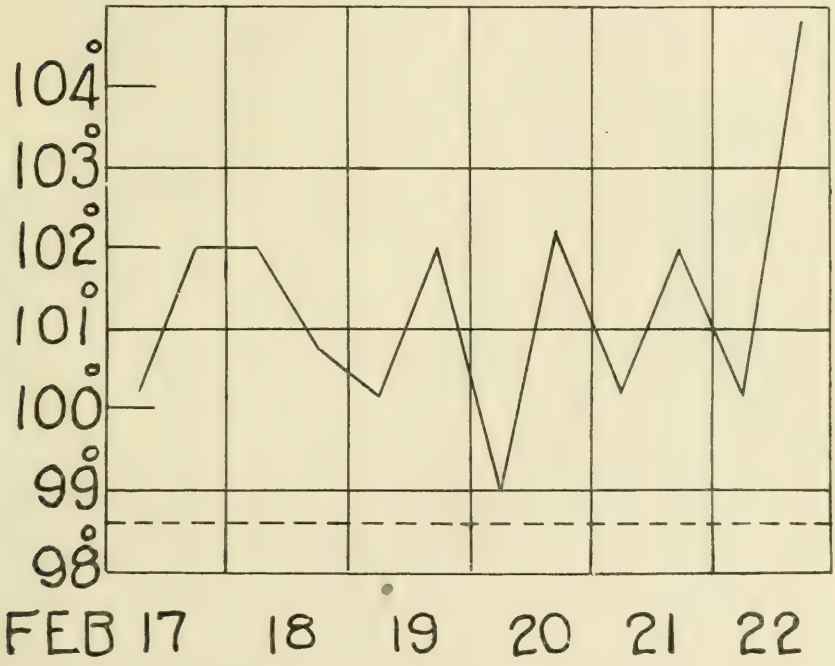

Fig. 11.—Temperature chart of John S.

120, rhythm regular. Pulse was dicrotic. Blood pressure: Systolic, 105 mm.; diastolic, 60 mm. Liver was not felt. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Blood: Leukocyte count on admission was 14,200, of which 84 per cent. were polymorphonuclears, 4.5 per cent. large mononuclears, 1.5 per cent. transitionals, 9.5 per cent. lymphocytes. Red cell count was 4,152,000. Hemoglobin, 75 per cent. Urine examination was negative.

He was studied in the calorimeter February 17, at which time his basal metabolism was found to be 14 per cent. above the average normal, with temperature falling between 37.8 and 37.4 C. On a second occasion the observation was unsuccessful because he was eliminating water from the skin and lungs at the rate of about 72 gm. per hour, which surpassed the capacity for ventilation of the calorimeter.

Case 14.—George M. *Pulmonary tuberculosis, with cavitation.*

History.—A machinist's helper, aged 31 years, was admitted March 15, 1920, complaining of chills, fever and night sweats and severe cough. In childhood he had whooping cough and measles at the age of 9 years. He was in perfect health until he went to India in 1917 in the transport service of the Mesopotamia campaign. While there he had "sand fly fever," for which he was treated with quinin. He also had dysentery which became chronic. Each winter following 1914 he had colds and persistent cough, nevertheless remaining in fairly good health. His appetite was habitually poor. He had a soft chancre in 1911 and later had gonorrhea also. He has had no secondary manifestations of syphilis. His maximum weight was 137 pounds.

In the winter of 1919-1920 the patient had his usual winter cough, but it was much more severe than usual. It kept him awake at night. He became very weak and "run down." Sputum was never bloody. About February 15 he began to feel chilly in the afternoon and at night he had severe sweats.

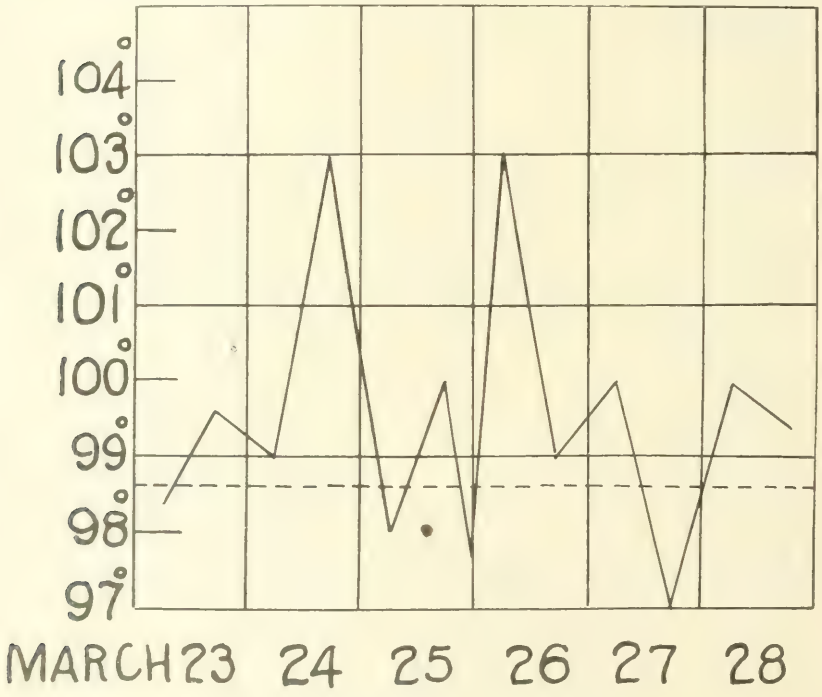

Fig. 12.—Temperature chart of George M.

His cough became worse and the expectoration blood tinged. He had had much substernal and precordial pain, aggravated by coughing. Vomiting was sometimes induced by the severity of the cough.

Physical Examination.—The patient was a small, thin man, 165 cm. tall, weighing 49.1 kg. Thorax of normal shape, but with marked supraclavicular retractions. Respiratory excursions were symmetrical and apparently not limited. Lungs: Both apices quite dull on percussion from the third rib in front to the angles of the scapulae behind. Over the dull areas there was increased fremitus and whispered voice transmission, bronchial breathing and many fine râles. At the right apex the breathing approached amphoric in quality, especially at the extreme upper part of the right axilla. The bases were slightly dull posteriorly and the excursion of neither base exceeded one finger's breadth.

There was bronchovesicular breathing at the right base and a few coarse râles were heard at both bases. Heart not enlarged nor displaced; rate 100; rhythm regular. Blood pressure: Systolic, 85 mm. There were a few palpable nodes in both inguinal regions. Moderate clubbing of fingers. Further findings were negative.

Laboratory Examination.—Sputum examination showed many tubercle bacilli. Urine normal. Blood: Leukocyte count (March 17), 11,400, of which 60 per cent. were polymorphonuclears, 29 per cent. lymphocytes, 9 per cent. large mononuclears, 1 per cent. transitionals, 1 per cent. eosinophils. March 26: Leukocytes, 11,000; polymorphonuclears, 73 per cent.; lymphocytes, 17 per cent.; large mononuclears, 10 per cent.

Vital capacity, average six trials, 2,523 c.c., which is 61 per cent. of the normal, as calculated by the method of West from the surface area.

This patient was observed in the calorimeter March 24 while the temperature was falling rapidly from 39.56 to 38.72 C., with sweating. The metabolism in the first hour was 34 per cent. above the average normal and during the second it was 27 per cent. above. March 26 another observation was made while the temperature fell from 39.23 to 38.17 C., the metabolism being 29 per cent. above the average normal. The percentage of heat lost through vaporization was from 32 to 35 per cent. of the total heat eliminated. This latter observation is graphically represented in Figure 14. The conditions were not basal in either case, due to restlessness.

Case 15.—Joseph R. *Pulmonary tuberculosis with cavitation; chronic nephritis with hypertension.*

History.—A printer, aged 36 years, was admitted May 3, 1920, complaining of "kidney trouble." While his health, in general, had always been good, he had had for a long time a slight, hacking cough, not productive, believed to be due to excessive smoking. He had been a heavy beer drinker. For many years he had urinated once during the night. His maximum weight was 180 pounds. In 1918 he lost weight rapidly to 161 pounds. His weight remained at 160 until six weeks before admission, when he again began to lose. Weight while in hospital was 134 pounds. About one week before admission he noticed swelling of the ankles and legs, extending within the next few days to the trunk and face. He felt nauseated and had some attacks of vomiting. He then began to urinate five or six times a night. He had not been conscious of fever and had had no night sweats. His cough had become productive, but there had been no hemoptysis.

Physical Examination on Admission.—Height, 175 cm.; weight, 61.13 kg. Patient was a well developed but rather poorly nourished man; lips somewhat cyanotic. He showed slight dyspnea, but sat up in bed reading comfortably. There was a slight venous pulsation in the neck. Chest was of normal shape and size. There were moderate retractions of the upper left side, seen chiefly in the second and third intercostal spaces. Lungs: Marked diminution of resonance over the whole left chest, with hyperresonance of the right. The upper left chest anteriorly was almost flat and fremitus was increased. Over this area the breath sounds were somewhat amphoric in quality. Elsewhere on the left the expiration was prolonged and high pitched. Heart: There was a general heaving of the precordium. The apex impulse was of maximum intensity in the fifth intercostal space 12 cm. to the left of the midline. The cardiac dulness extended from the right sternal margin to 14 cm. to the left in the fifth intercostal space. Rhythm was regular. There were no murmurs. There was slight accentuation of the aortic second sound. Blood pressure: Systolic, 160 mm.; diastolic, 120 mm. Arteries not thickened. Abdomen was somewhat distended and tender in the right upper quadrant. Liver was felt three fingers' breadth below the costal margin. Hands were somewhat cyanotic and puffy, but did not pit. There was some edema of both lower extremities and under the sacrum.

Laboratory Examination.—The urine showed a low specific gravity (1.010), considerable albumin, no sugar, many hyalin and granular casts, many red blood cells and many clumped leukocytes. Blood: May 4, leukocytes, 10,000; hemoglobin, 70 per cent.; May 6: nonprotein nitrogen, 39.5 mg. per hundred c.c.; creatinin, 1.7 mg. per hundred c.c. May 5 the sputum contained many tubercle bacilli.

The patient improved rapidly. May 12 the dyspnea was almost gone; edema very slight. The roentgen ray showed pulmonic fields of unequal size, the right being larger than the left. There was marked diminution of the illumination throughout the entire left pulmonic field, and the middle third of the right. Costophrenic spaces were clear. There was increase in size and density of the right hilum shadow. There was increase in size, number and density of the left pulmonic and also of the middle third of the right field, markings agglutinated throughout. Large cavity at the left apex. Diaphragm shadow normal. Heart enlarged, distorted in appearance, with adhesions. Fibrosis, infiltration and cavitation of the left lung, tuberculosis.

May 24 there was no edema or dyspnea. Blood pressure: Systolic, 128 mm.; diastolic, 110 mm. Fundus of each eye normal. Comfortable.

May 25 he was studied in the calorimeter. Rectal temperature 36.7 C. His heat production was 70.7 calories per hour, or 40.5 calories per square meter per hour, being 3 per cent. above the average normal. He was then studied in the metabolism ward. The diet given is shown in Table 6 and graphically in Figure 19.

May 26 the nonprotein nitrogen content of the blood was 26 mg. per hundred c.c.

June 1, 1920, a cystoscopy was done. The cystoscope passed easily into the bladder and some clear urine was obtained. Bladder capacity normal. Bladder neck and fundus normal, but many trabeculations were seen on the posterior bladder wall. Mucosa normal. Both ureteral orifices were normal. Specimens were obtained from both sides, but no further report was made.

TABLE 6.—Diet Chart and Nitrogen Balance in Case 15

Name and Date	Total Calories	Carbohydrate, Gm.	Fat, Gm.	Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Wt., Kg.	Urine Vol., C.c.	Water Intake, C.c.	NaCl Intake Gm.	Urine NaCl Gm.
Joseph R.												
5/15/20	1,678	165	83	9.1	9.5	10.5	—1.4	64.0	2,155	1,900	7.61	
5/16/20	1,886	183	92	10.8	10.6	11.6	—0.8	....	2,080	1,990	7.61	
5/17/20	1,823	189	85	10.0	10.7	11.7	—1.7	62.5	2,030	2,000	7.99	8.48
5/18/20	1,992	229	85	10.2	8.0	9.0	+1.2	61.8	2,210	2,224	7.45	9.57
5/19/20	2,261	277	94	10.0	8.2	9.2	+0.8	....	1,630	2,000	7.26	6.15
5/20/20	2,002	250	78	9.9	8.1	9.1	+0.8	....	1,740	2,000	7.23	6.80
5/21/20	1,914	220	86	8.3	7.6	8.6	—0.3	62.0	2,135	2,000	7.40	7.29
5/22/20	2,248	238	123	4.9	7.6	8.6	—3.7	....	2,135	2,000	7.66	7.29
5/23/20	1,998	218	93	4.6	5.6	6.6	—2.0	....	2,155	2,000	6.85	8.32
5/24/20	2,085	269	93	4.8	5.7	6.7	—1.9	62.3	2,350	2,000	6.94	9.13
5/25/20	1,772	251	67	4.6	5.1	6.1	—1.5	61.3	1,930	2,000	6.87	8.06
5/26/20	2,370	302	113	3.4	5.1	6.1	—2.7	....	2,580	2,000	6.58	11.15
5/27/20	2,510	332	114	3.3	4.3	5.3	—2.0	60.8	2,520	2,000	6.33	10.96
5/28/20	2,493	327	115	3.3	2.5	3.5	—0.2	60.4	1,480	2,000	6.54	5.50
5/29/20	2,555	342	115	3.4	4.3	5.3	—1.9	....	2,380	2,000	6.55	9.26
5/30/20	2,493	327	115	3.3	3.9	4.9	—1.6	59.4	2,455	2,000	6.54	8.59

* Estimated.

Comment.—The tendency to retain nitrogen in the blood in this case is negligible. The nonprotein nitrogen of the blood before beginning the diet was 39.5 mg. per hundred c.c., while on May 20, before the food nitrogen was reduced, the nonprotein nitrogen was only 26 mg. per hundred c.c. The explanation of the loss in weight becomes apparent at once on examination of the intake and output of salt and water. The weight declined as an excess of salt and water were eliminated, and the edema disappeared.

DISCUSSION OF RESULTS

The results of the observations made in the calorimeter are shown in Table 7. The respiratory quotients are all within normal limits. The average quotient for fasting [25] observations is 0.79, so that there is no evidence of a qualitative change in the combustions as far as the respiratory quotients are concerned.

Regarding quantitative changes in the metabolism, the data are presented from two points of view in Table 8. It is customary to compare the observed heat production of a patient with the theoretical heat production of a normal man of the same surface area. The percentage variation from the average normal metabolism is shown. It will be observed that in only ten of the fifteen cases were there observations which were considered basal; that is, in the condition of complete rest in the fasting state. The conception of the basal metabolism on which this was based implies the minimal metabolism. If the patient had fever at the time of observation it was considered basal only if the temperature was approximately at the lowest part of the diurnal variation. In the case of Robert W., the patient was very quiet at a temperature of about 40 C. This was not considered basal because the temperature was near the peak of the diurnal curve. In the first hour of the observation on Trellis H. the patient was also very quiet at a similar temperature. If one considers these as basal periods then it may be said that the basal metabolism at 40 C. is 28 or 29 per cent. above the average normal. In the ten remaining cases the basal metabolism ranges from 3 per cent. below to 15 per cent. above the average normal. Barbour's three cases lie within this range, so that it appears that the basal metabolism, as conceived above, is but very slightly elevated above that of normal men of the same surface area.

It should be remembered, however, that in losing weight the surface area of the patient has diminished. As far as each individual patient is concerned, the normal metabolism is the metabolism in health. Comparison of the present with the probable normal metabolism has been made and is also shown in Table 8, for each case in which the previous weight of the patient was known. It will be observed that in all cases except one, John S., the average hourly basal heat production observed is equal to or less than the estimated calories per hour for the same patient in health. In the case of John S. the increase is slight.

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25. Not strictly fasting; small standard breakfast, previously referred to,[9] was given. The effect of this may be considered negligible.

TABLE 7.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Chas. G.	Prelim.	12:26	....	....	....	....	....	....	....
5/8/17	1	1:26	22.2	21.0	0.77	30.5	0.30	....	62.2
52.2 Kg.	2	2:26	22.6	21.0	0.78	30.6	0.30	....	65.7
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	69.7	....
Chas. G.	Prelim.	12:10	....	....	....	....	....	....	....
5/11/17	1	1:10	23.0	20.2	0.83	28.4	0.33	....	66.3
52.7 Kg.	2	2:10	23.2	21.7	0.78	38.0	0.33	....	77.2
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	69.8	....
Chas. G.	Prelim.	11:58	....	....	....	....	....	....	....
5/14/17	1	12:58	22.5	20.2	0.81	47.7	0.31	....	73.1
52.4 Kg.	2	1:58	23.0	20.4	0.82	39.7	0.31	....	70.0
1.57 Sq. M.	3	2:58	22.9	21.3	0.78	42.7	0.31	....	73.5
	4	3:35	13.8	12.7					
	Aver.	.....	....	....	....	....	....	68.8	....
Trellis H.	Prelim.	11:47	....	....	....	....	....	....	....
5/9/17	1	12:47	29.7	26.6	0.81	40.1	0.44	98.0	78.4
51.7 Kg.	2	1:47	26.4	24.2	0.79	33.5	0.44	80.2	74.8
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Robert W.	Prelim.	11:18	....	....	....	....	....	....	....
5/25/17	1	12:18	26.3	23.7	0.81	36.5	0.57	....	72.1
53.4 Kg.	2	1:18	25.6	25.3	0.74	42.1	0.57	....	73.3
1.57 Sq. M.	3	2:18	25.2	23.1	0.80	49.4	0.57	....	93.5
	Aver.	.....	....	....	....	....	....	78.6	....
Geo. P.	Prelim.	12:07	....	....	....	....	....	....	....
5/24/17	1	1:07	23.8	21.8	0.79	32.3	0.27	72.7	66.0
58.5 Kg.	2	2:10*	25.9	23.4	0.80	32.8	0.27	78.3	69.7
1.70 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Spencer C.	Prelim.	11:41	....	....	....	....	....	....	....
12/10/19	1	12:41	22.6	18.4	0.89	28.1	....	62.8	54.8
44.3 Kg.	2	1:41	23.1	19.1	0.88	30.4	....	65.0	58.5
1.48 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	12:47	....	....	....	....	....	....	....
12/17/19	1	1:47	19.5	17.3	0.82	21.9	....	57.9	49.1
44.6 Kg.	2	2:47	19.8	18.0	0.80	21.6	....	60.2	47.3
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	8:50 p.m.	....	....	....	....	....	....	....
12/19/19	1	9:50	19.6	19.1	0.75	31.6	....	62.8	61.2
45.5 Kg.	2	10:50	23.9	21.2	0.82	31.1	....	71.2	60.5
1.53 Sq. M.	3	11:50	23.2	21.6	0.78	34.6	....	71.7	71.0
	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	2:42 p.m.	....	....	....	....	....	....	....
1/6/20	1	3:42	22.9	21.0	0.79	27.0	0.07	70.2	59.8
44.0 Kg.	2	4:42	22.2	20.6	0.78	27.9	0.07	68.9	63.7
1.53 Sq. M.	3	5:42	22.6	21.0	0.78	31.0	0.07	70.1	69.1
	Aver.	.....	....	....	....	....	....	....	....
Harry G.	Prelim.	12:38	....	....	....	....	....	....	....
1/13/20	1	1:38	23.6	21.5	0.80	39.4	....	71.8	78.2
42.8 Kg.	2	2:38	24.1	22.6	0.77	38.1	....	75.0	71.5
1.49 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Joseph D.	Prelim.	12:12	....	....	....	....	....	....	....
1/17/20	1	1:12	20.5	17.9	0.83	26.0	0.17	60.4	58.5
59.0 Kg.	2	2:12	21.8	21.0	0.76	29.8	0.17	69.3	67.9
1.74 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Mabel C.	Prelim.	11:50	....	....	....	....	....	....	....
1/20/20	1	12:50	26.5	25.2	0.76	41.5	0.05	83.8	82.3
50.0 Kg.	2	1:50	25.7	23.6	0.79	42.5	0.05	79.1	81.6
1.62 Sq. M.	Aver.	.....	....	....	....	....	....	....	....

-Calorimetric Data

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	37.8	...	....	....	..	..	..	....	....	Basal
64.4	37.9	...	4.0							
67.0	37.9	...	6.5							
....	....	116	....	0.77	11	70	19	1.34	44.4	
....	38.6	...	....	....	..	..	..	....	....	Falling temperature
57.2	38.4	...	11.0							
68.6	38.2	...	18.0							
....	....	129	....	0.80	13	59	28	1.33	44.5	
....	38.1	...	....	....	..	..	..	....	....	Basal
60.4	37.8	...	2.5							
73.0	37.9	...	7.5							
70.8	37.8	...	8.0							
....	....	118	....	0.80	12	60	29	1.31	43.8	
....	39.7	...	....	....	..	..	..	....	....	Rising temperature
93.1	40.1	...	18.5	0.81	12	56	32	1.90	62.4	
78.8	40.2	...	....	0.80	15	59	26	1.55	51.1	
....	....	90								
....	40.1	...	....	....	..	..	..	....	....	High temperature, very quiet
65.9	40.0	...	2.5							
68.2	39.6	...	4.5							
80.5	39.4	...	3.0							
....	....	104	....	0.73	19	73	8	1.47	50.1	
....	37.4	...	....	....	..	..	..	....	..	(* 63 min.) Basal; very quiet; work adder broken
75.4	37.6	...	....	0.79	10	64	26			
76.6	37.8	...	....	0.80	10	60	30			
....	....	70	....	....	..	..	..	1.26	43.3	
....	36.6	...	....	....	..	..	..	....	....	Basal
57.8	36.6	...	24.2	....	..	..	..	1.42	42.4	
57.0	36.6	...	1.3	....	..	..	..	1.47	43.9	
....	....	93								
....	37.3	...	....	....	..	..	..	....	....	Basal
67.0	37.8	...	23.0	....	..	..	..	1.30	37.8	
67.0	38.3	...	23.0	....	..	..	..	1.35	39.3	
....	....	116								
....	39.5	...	....	....	..	..	..	....	....	High fever, restless in last hour, quiet in first hour
71.4	39.8	...	25.0	....	..	..	..	1.38	41.0	
65.5	39.9	...	21.0	....	..	..	..	1.57	46.5	
70.0	39.6	...	58.7	....	..	..	..	1.58	46.8	
....	....	125								
....	39.9	...	....	....	..	..	..	....	....	High temperature, coughing
68.5	40.1	...	40.0	0.79	2	68	30	1.64	47.1	
75.0	40.4	...	27.0	0.78	2	73	25	1.56	45.0	
53.1	40.0	...	33.0	0.78	2	72	26	1.60	45.8	
....	....	137								
....	39.2	...	....	....	..	..	..	....	....	Observation vitiated by restlessness
69.0	39.0	...	45.0	....	..	..	..	1.68	51.3	
69.7	38.9	...	43.0	....	..	..	..	1.68	51.4	
....	....	120								
....	37.2	...	....	....	..	..	..	....	....	Afebrile, basal, moved in last 4 min. of last period
58.2	37.2	...	39.5	0.84	8	52	40	1.02	34.7	
70.5	37.2	...	50.0	0.75	7	77	16	1.17	39.9	
....	....	82								
....	39.8	...	....	....	..	..	..	....	....	Restless, coughing
65.2	39.4	...	43.0	0.76	2	80	18	1.68	51.7	
4.4	39.2	...	36.0	0.79	2	70	28	1.58	48.8	
....	....	120								

TABLE 7.—CALORIMETRIC—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Anna H.	Prelim.	12:25	....	....	....	....	....	....	....
2/5/20	1	1:25							
41.0 Kg.	2	2:25	45.5	47.3	0.76	62 9	0.46	143.9	138.2
1.41 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	11:50	....	....	....	....	....	....	....
2/10/20	1	12:50	21.6	20.1	0.78	37.5	....	66.8	69.0
45.5 Kg.	2	1:55*	23.9	23.7	0.73	35.3	....	77.8	71.9
1.53 Sq. M.									
John H.	Prelim.	11:54	....	....	....	....	....	....	....
2/12/20	1	12:54	24.1	23.4	0.75	34.6	0.42	76.6	71.6
45.1 Kg.	2	1:54	25.5	25.1	0.74	40.3	0.42	82.2	77.7
1.53 Sq. M.	3	2:54	26.5	26.5	0.73	43.6	0.42	86.5	81.7
	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	1:19	....	....	....	....	....	....	....
3/1/20	1	2:19	21.4	21.6	0.72	30.6	....	70.5	63.9
44.9 Kg.									
1.53 Sq. M.									
John H.	Prelim.	1:22	....	....	....	....	....	....	....
4/14/20	1	2:22	19.9	17.8	0.82	48.9	....	59.6	75.2
44.7 Kg.	2	3:22	20.8	20.0	0.76	47.2	....	66.3	69.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:15	....	....	....	....	....	....	....
3/2/20	1	1:15	23.0	21.5	0.78	34.9	0.34	71.2	76.6
50.3 Kg.	2	2:15	23.2	22.6	0.75	33.8	0.34	74.2	75.5
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:00	....	....	....	....	....	....	....
3/10/20	1	1:00	20.8	19.4	0.78	31.4	0.30	64.4	72.1
49.7 Kg.	2	2:00	21.5	20.2	0.78	30.3	0.30	66.8	70.6
1.53 Sq. M.									
Wm. H.	Prelim.	11:27	....	....	....	....	....	....	....
3/11/20	1	12:27	21.8	21.0	0.75	40.0	0.65	68.7	73.1
49.7 Kg.	2	1:27	24.0	22.5	0.77	32.4	0.65	73.9	70.5
1.53 Sq. M.	3	2:27	27.4	26.3	0.76	33.9	0.65	86.1	76.1
	Aver.	.....	....	....	....	....	....	....	....
John S.	Prelim.	12:37	....	....	....	....	....	....	....
3/17/20	1	1:37	26.9	22.9	0.86	41.4	....	77.6	83.6
62.3 Kg.	2	2:37	27.1	28.0	0.71	51.9	....	91.5	92.3
1.88 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:20	....	....	....	....	....	....	....
3/24/20	1	12:20	26.1	24.3	0.78	41.5	....	80.8	81.2
49.2 Kg.	2	1:22*	25.1	22.6	0.81	48.0	....	76.1	90.4
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:22	....	....	....	....	....	....	....
3/26/20	1	12:22	27.4	23.1	0.86	43.9	....	78.4	80.0
48.9 Kg.	2	1:22	25.8	23.2	0.81	61.6	....	77.5	101.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Joseph R.	Prelim.	12:27	....	....	....	....	....	....	....
5/25/20	1	1:27	23.5	21.2	0.81	29.7	0.20	71.0	60.5
61.3 Kg.	2	2:27	23.1	21.1	0.80	29.5	0.20	70.4	64.1
1.74 Sq. M.	Aver.	.....	....	....	....	....	....	....	....

—DATA—(*Continued*)

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	39.4									
	39.5	...	21.0							
146.3	39.6	...	21.0	0.74	17	73	10	....	....	Fairly quiet
....	....	132	....	....	..	..	..	1.76	51.1	
....	37.4	...	....	....	..	..	..	....	....	(* 65 min.) Basal
65.2	37.3	...	8.5	....	..	..	..	1.47	43.7	
74.6	37.4	...	11.0	....	..	..	..	1.57	46.7	
....	37.9	...	....	....	..	..	..	....	....	350 gm. meat given 1 hour before start
72.0	37.9	...	30.0	0.74	15	75	10	1.70	50.0	
79.5	38.0	...	20.0	0.73	14	79	7	1.82	53.7	
84.2	38.1	...	37.0	0.72	13	57	30	1.92	56.5	
....	....	93								
....	38.7	...	....	....	..	..	..	....	....	Basal
64.6	38.7	...	18.0	....	..	..	..	1.57	46.1	
....	37.8	...	....	....	..	..	..	....	....	Basal
60.5	37.4	...	3.0	....	..	..	..	1.33	39.0	
72.4	37.5	...	11.0	....	..	..	..	1.48	43.3	
....	....	104								
....	38.6	...	....	....	..	..	..	....	....	Basal in first hour, coughing in second hour
76.3	38.6	...	18.5	0.78	13	67	20	1.41	46.5	
75.9	38.6	...	35.5	0.74	12	78	10	1.47	48.5	
....	....	80								
....	38.0	...	....	....	..	..	..	....	....	Basal
72.2	38.0	...	8.5	0.78	12	68	20	1.32	42.1	
71.0	38.0	...	11.0	0.77	12	69	19	1.49	48.5	
....	37.6	...	....	....	..	..	..	....	....	350 gm. meat given 1 hour before start
64.0	37.4	...	3.5	0.74	23	70	7	1.38	44.9	
76.3	37.5	...	14.0	0.76	20	65	15	1.49	48.3	
88.1	37.8	...	24.0	0.75	25	66	9	1.73	56.3	
....	....	85								
....	37.8	...	....	....	..	..	..	....	....	Basal
83.7	37.9	...	10.0	....	..	..	..	1.25	41.3	
69.4	37.4	...	32.0	....	..	..	..	1.47	48.7	
....	....	114								
....	39.6	...	....	....	..	..	..	....	....	(* 62 min.) Falling temperature, restless
74.5	39.4	...	25.0	....	..	..	..	1.64	52.8	
61.8	38.7	...	30.0	....	..	..	..	1.46	48.1	
....	....	94								
....	39.2	...	....	....	..	..	..	....	....	Rapid fall of temperature, restless
63.3	38.8	...	40.0	....	..	..	..	1.60	51.2	
74.2	38.2	...	40.0	....	..	..	..	1.59	50.6	
....	...	84								
....	36.7	...	....	....	..	..	..	....	....	Basal
62.2	36.8	...	17.0	0.81	8	60	32	1.16	40.8	
58.7	36.7	...	12.0	0.80	8	64	28	1.15	40.5	
....	....	88								

In the remaining observations, which were not basal, it will be observed in Table 8 that the heat production may be considerably increased by coughing, restlessness and by high fever. The increase in metabolism is usually due to several factors combined and it is, of course, impossible to evaluate each factor. The greatest increase in any single hour reached 43 per cent. above the average normal in the case of Trellis H., whose temperature was over 40 C. and who was coughing. In one observation on William H. the temperature remained stationary at 38.6 C. during two hours in the first of which

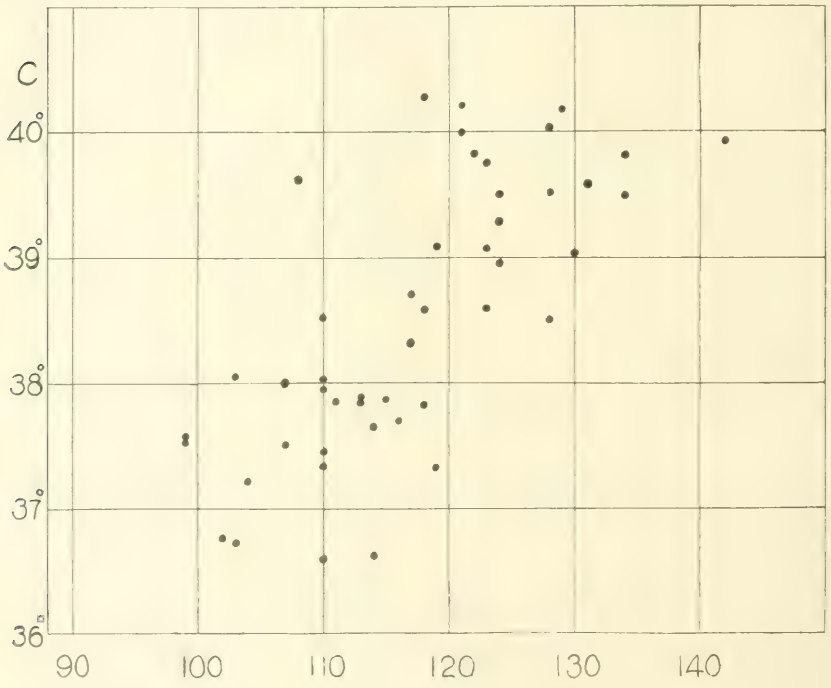

Fig. 13.—Relationship of body temperature and heat production in tuberculosis. The metabolism, during a short period, expressed in terms of percentage of average normal (100 per cent.) is plotted against the mean rectal temperature for the same period, which was usually one hour.

the patient was very quiet and the metabolism was 18 per cent. above the average normal. In the second hour he was likewise very quiet but coughed considerably, with the result that a further increase of 5 per cent. in metabolism occurred.

In Figure 13 an attempt has been made to evaluate the effect of body temperature on the heat production. In the figure the spots represent the percentage of average normal metabolism in a given period, usually one hour, plotted against the average rectal temperature for the period. The grouping of these points suggests the

general tendency of an increased body temperature to increase the heat production. In the case of Robert W. the patient was very quiet at a temperature ranging between 40.1 and 39.4 C., the metabolism being 29 per cent. above average normal. Also, in one hour Trellis H. was very quiet, with a temperature of from 40.1 to 40.2 C., his metabolism being 29 per cent. above average normal. In these two cases the effect of temperature is uncomplicated.

In Figure 14 there is a graphic representation of the relationship of heat produced in the body to the heat eliminated from the body in five cases, chosen to illustrate different phases of temperature change. In the case of Edith B., the temperature rose from 37.3 C. to 38.3 C. during two hours, without a chill. It will be observed that during this rise of 1 degree the heat production rose only a little over two calories per hour. During the first hour the heat eliminated was 9 calories less than the heat produced, and during the second hour the elimination of heat was about 2 calories less than in the first, still further increasing the storage of heat.

The question of the mechanism of temperature changes in the body is of great interest. A review of the literature on this subject will be found in a paper by Barr and Du Bois.[26] In the metabolism of malaria the rise in temperature was accompanied by a chill and a part of the rise in heat production may therefore be attributed to the muscular work of shivering. The case of Edith B., therefore, may be contrasted with the malarial paroxysm, since in her case the rise was not accomplished by a chill, nor by much increase in metabolism, the heat radiated being reduced. Referring again to Figure 14, it will be noticed that on a subsequent occasion with a much higher temperature her metabolism during the first hour showed almost no further increase over that of the first observation. During the second and third hours she was coughing and restless. These observations show that increases in metabolism due to elevation of body temperature, per se, may not be large.

In this same observation and in a subsequent one on the same patient the peak of the rise in rectal temperature was included. Though the rectal temperature had started to drop in the third hour of each experiment, the heat eliminated from the body had not yet exceeded the heat produced. Thus, it appears that for a short time, at least, the average body temperature was still rising after the rectal temperature began to fall.

The fourth observation, graphically presented in Figure 14, shows a rapid fall of temperature with sweating. Here the heat lost greatly

26. Barr, D. P., and Du Bois, E. F.: The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

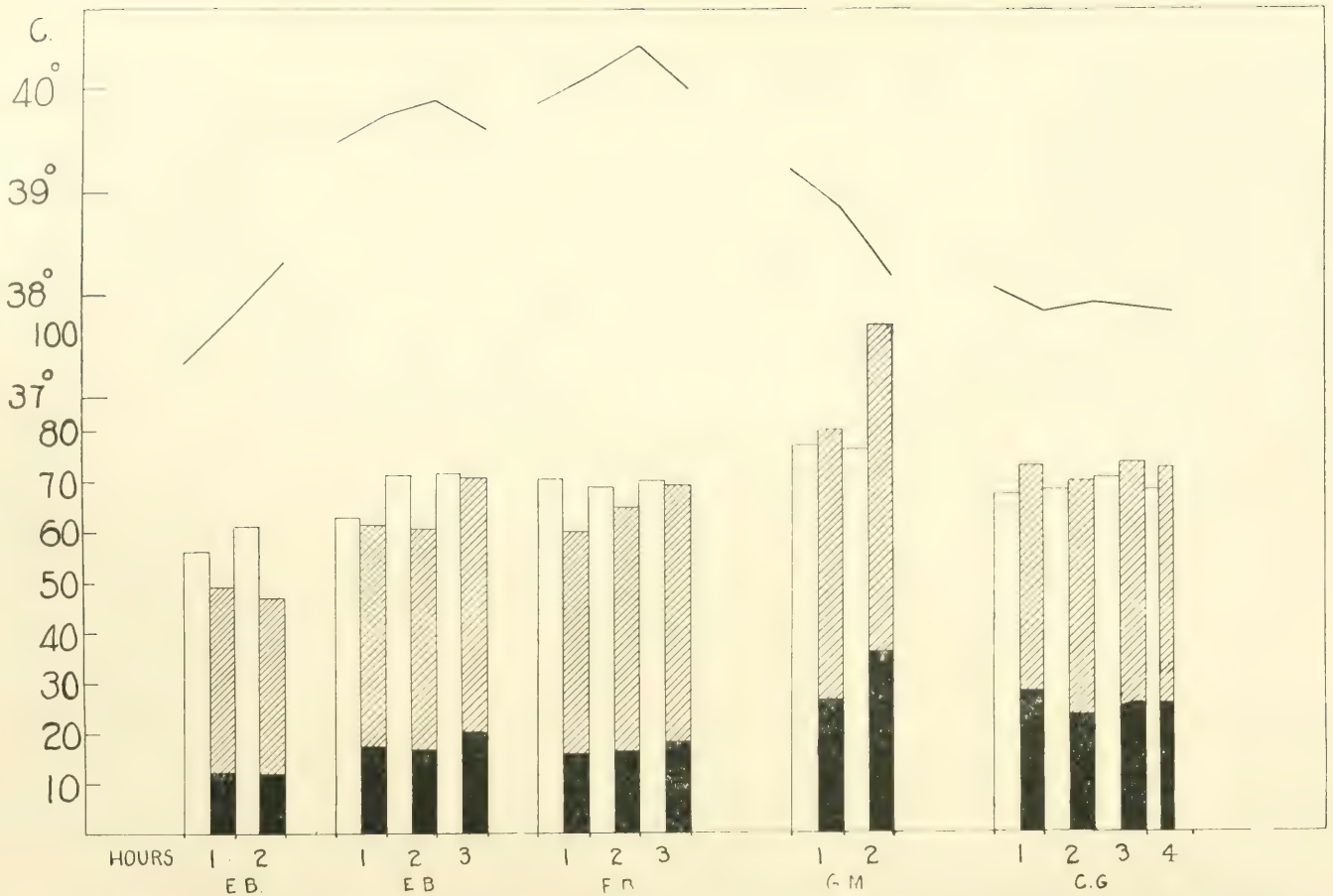

Fig. 14.—Relationship of heat production and heat elimination during rise and fall of rectal temperature. Five observations on three individuals. Lines show rectal temperature in degrees C. Unshaded columns represent calories per hour produced in the body, determined by the indirect method. Shaded columns represent heat lost from the body by vaporization of water (solid black) and by radiation (hatched). Periods are one hour for each pair of columns.

exceeded the heat produced, and the average body temperature fell with the rectal temperature. In this observation a great increase occurred in the number and percentage of calories lost by vaporization of water from the skin and lungs. Du Bois [27] has shown that under ordinary circumstances the water elimination from these sources requires about 25 per cent. of the total heat for its vaporization. In the case of George M. the percentage was between 32 and 35. In the observation of Charles G., shown in the same figure, the latent heat of vaporization amounts to 38 per cent. of the total. This observation was made at the end of a fall in temperature and it will be noted that the average body temperature continued falling after the rectal temperature had become almost stationary. These observations show that the rectal temperature is not an entirely reliable index of changes of the average body temperature and that the absolute relation between the two remains unknown.

In this connection it should be pointed out that the heat produced, as calculated in the direct calorimetry, is equal to the heat eliminated plus or minus the body change correction. This body change correction is estimated by multiplying the change in rectal temperature in degrees centigrade by the specific heat of the body (0.83) times the body weight in kilograms. For the year 1919-1920 the total number of calories measured indirectly was 6,511.73, the total heat eliminated was 6,441.60 calories, while the total heat produced measured by the direct calorimetry, corrected for changes in rectal temperature, was 6,167.37. Such a discrepancy may be accounted for partly by the lack of parallelism between the rectal and average body temperatures and the fact that the total fall in rectal temperature exceeded the total rise.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN TUBERCULOSIS

Two of the patients in this series were given a meal of meat in order to study the effect of the protein on the heat production. Various meals have been used in the past for this purpose, but in the present instance the meal consisted of 350 gm. of lean beef, ground, pressed into balls, and cooked in 10 gm. of butter. This gave 70 gm. of protein, 28 gm. of fat and 547 total calories. The observation in each case was started one hour after the middle of the meal and continued for three hours. The rise in heat production compared with the basal heat production is shown graphically in Figure 15..

The average increase in metabolism per hour for three hours was 16.1 per cent. in the case of William H. and 18.4 per cent. in

27. Soderstrom, G. F., and Du Bois, E. F.: The Water Elimination Through the Skin and Respiratory Passages, Arch. Int. Med. **19**:931 (June) 1917.

the case of John H. In the first case the extra heat in the fourth hour after eating amounted to 31 per cent. of the basal metabolism and in the second case to 25 per cent. The effect of the same meal has been studied on three normal men. So far, the behavior of the tuberculous patients has differed in no way from that of normals. Further study of the effect of this protein meal, both on tuberculous and normal subjects, will be the subject of a later communication.

With the normal subject with the same meal the average percentage increases in the second, third and fourth hours, respectively, were 16, 24 and 24 per cent. The average increase per hour was 21 per cent. There were considerable variations among the normals studied, probably due to differences in the rate of digestion and absorption. The effect of the meal has been observed on one normal to the end of the fifth hour after eating, in which the metabolism

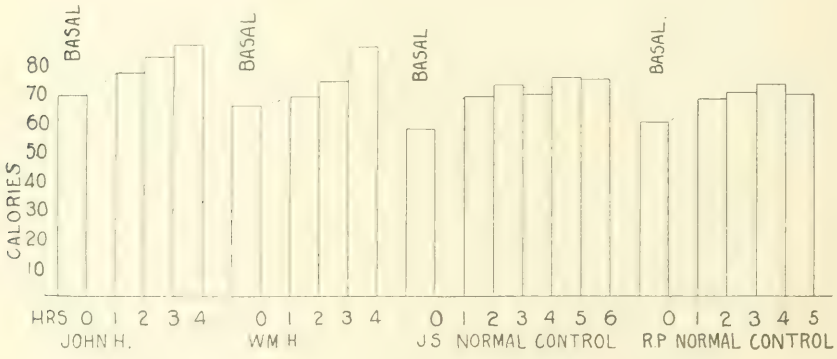

Fig. 15.—Effect of a protein meal on the heat production.

was still 30 per cent. above the basal level, with an average hourly increase of 25 per cent. It seems probable that the effect of the meal would persist for from nine to ten hours at least.

It is to be remembered that Coleman and Du Bois [28] found very little specific dynamic action of protein in febrile typhoid patients. They point out that the protein metabolism was at high level at the time of the basal observation, due to the influence of the disease, and that the protein ingested merely served to replace protein already breaking up in increased quantity, and such protein would not serve to increase the heat production. The fact that a specific dynamic rise has been noted in tuberculosis is further evidence that the toxic destruction of protein is less than in typhoid fever.

28. Coleman, Warren, and Du Bois, E. F.: Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med. **15**: Pt. 2, 940 (May) 1915.

THE PROTEIN MINIMUM IN TUBERCULOSIS

The minimum protein requirement in tuberculosis probably depends, as in health, on the size of the "wear and tear" quota and an adequate supply of nonprotein foodstuffs. Investigations of other infections have shown generally an increase in protein destruction due to the toxins of the disease. Some evidence [2] has been given regarding the extent of this toxic destruction, which indicates that it is small but of importance because of the great duration of the disease.

The work of Chittenden, Sivén, Kumagawa and many others [29] indicates that the protein metabolism of normal men may be reduced to a very low level. More recently Sherman [30] has found from 0.633 to 0.637 gm. of protein per kilogram of body weight per diem to be adequate for the maintenance of normal men.

In typhoid fever Kocher [31] has studied the toxic destruction of protein by giving to a patient a diet containing carbohydrate in large amounts and very little protein. He found it impossible, during the febrile period, to reduce the protein metabolism to the low level of the normal "wear and tear" quota.

In four of the cases of our series, observations were made which were somewhat similar to those of Kocher. The estimated daily basal requirement for each case is given in Table 8. The records of the amounts of food given and of the nitrogen balances are to be found in Tables 3 to 6, inclusive, and are shown graphically in Figures 16 to 19, inclusive. In general, the procedure was to give the patient a diet slightly in excess of the basal energy requirement, containing between 10 and 15 gm. of nitrogen per diem for a period of five or six days. The nitrogen intake was then reduced, with a simultaneous increase in the amount of fat and carbohydrate.

The data obtained in these four cases are insufficient to establish the minimum requirement of protein for tuberculous patients. They will serve as a starting point for work of a similar nature, on which a later report will be made. In general it may be said that when the food nitrogen was reduced to the low level of from 3 to 3.5 gm. per diem, with the addition of from 600 to 900 calories to the basal requirement, the urinary nitrogen excretion fell to the level of 5 or 6 gm. per diem, the patient remaining in negative nitrogen balance. This indicates a "wear and tear" quota greater than normal. The minimum nitrogen excretion noted by Kocher [31] in a typhoid patient was somewhat higher (10.4 gm. during fever, from 5.8 to 6.7 gm. beginning convalescence) and was obtained at the expense of much

29. Chittenden, Russell H.: Physiological Economy in Nutrition, 1914.
30. Sherman, H. C.: Protein Requirement in Maintenance of Man, J. Biol. Chem. **41**:97, 1920.
31. Kocher: Deutsch. Arch. f. klin. Med. **115**:106, 1914.

more carbohydrate and fat. A toxic destruction of protein exists, therefore, in tuberculosis but to less extent than in typhoid fever.

In view of the results in these four cases, it seems probable that many febrile, tuberculous patients may be kept in nitrogen balance on diets containing from 60 to 70 gm. of protein per diem. The

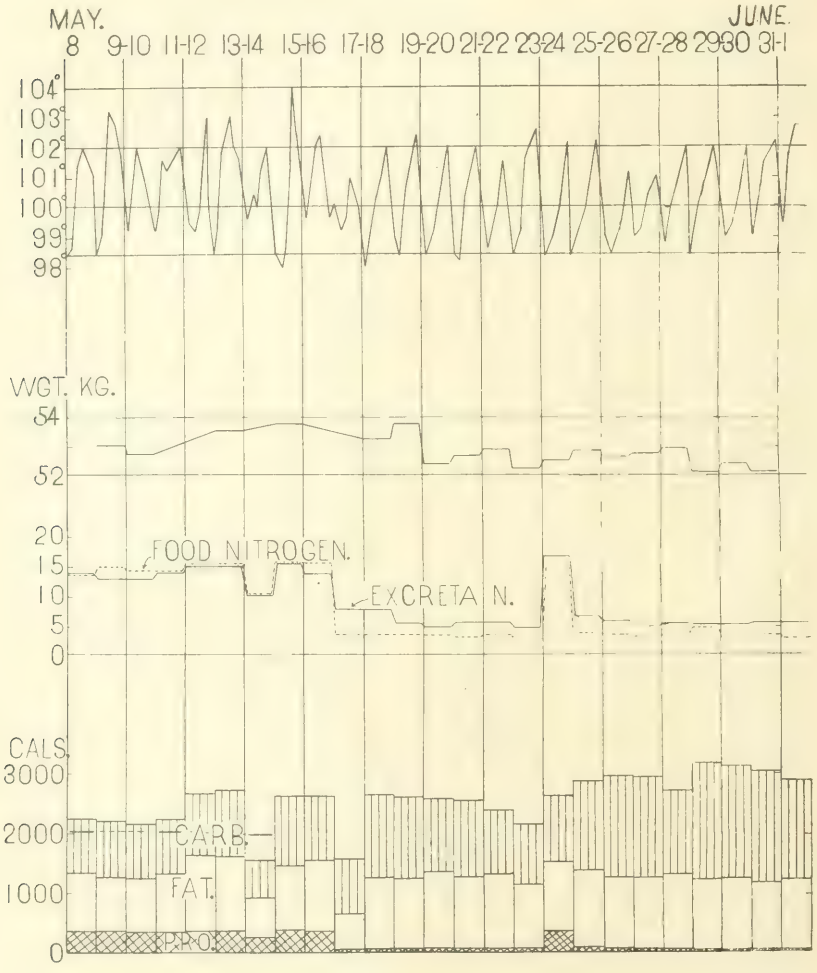

Fig. 16.—Diet chart and nitrogen balance, Charles G.

amount of protein is much less than Voit's standard allowance (118 gm.) for normal men, though somewhat greater than the normal minima of Chittenden and of Sherman (from 35 to 45 gm.). It is much less than is fed to patients in many of the sanitaria for tuberculosis.

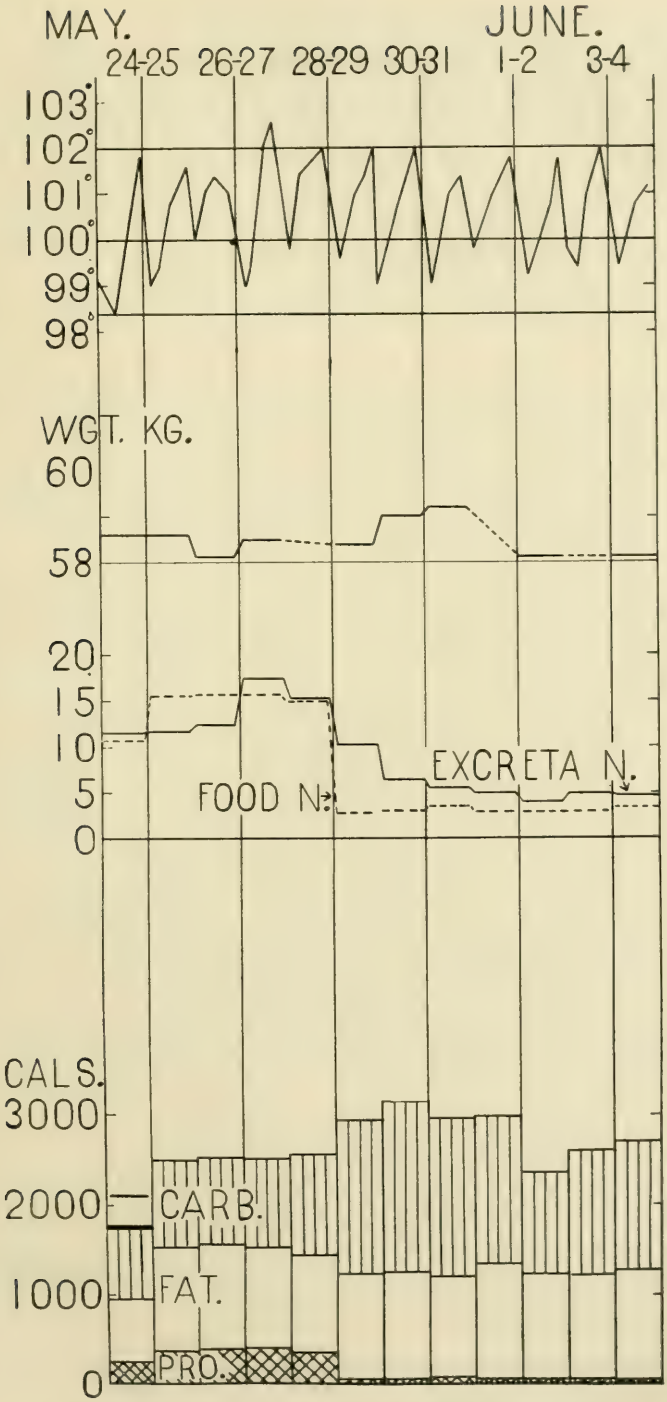

Fig. 17.—Diet chart and nitrogen balance, George P.

PRACTICAL CONSIDERATIONS REGARDING DIET IN TUBERCULOSIS

The importance of rest during periods of activity of pulmonary tuberculosis has been generally recognized. By artificial pneumothorax, by rest, by control of the cough, the volume of the respiratory exchange and of the total ventilation is reduced. This seems to be a desirable end for which to strive during the period of encapsulation of the foci of the disease. It does not seem to have occurred to the practitioner that an increase in metabolism due to the specific dynamic action of protein will have the same effect on the respiratory exchange as a similar increase due to muscular work.

TABLE 8.—Summary of Calorimeter Data

Name	Weight in Health, Kg.	Surface in Health, Sq. M.	Estimated Calories per Hour in Health	Present Calories per Hour Observed	Present Surface Area, Sq. M.	Metabolism Variation from Aver. Normal per Cent.	Calories per 24 Hours	Remarks
Chas. G.	....	. ..	. ..	69.5	1.56	+13	1 668	Basal
Trellis H.	....	....	....	84.4	1.57	+35	2,026	Fever, 40 C.; cough
Robert W.	.. .	....	....	78.6	1.57	+29	1,886	40.1-39.4 C., quiet
Geo. P.	69.5	1.84	75.4	75.5	1.70	+11	1,812	Basal
Spencer C.	74.0	1.85	71.2	63.9	1.48	+12	1,534	Basal
Edith B.	61.5	1.77	66.4	59.0	1.53	+ 2	.....	Basal, afebrile
				66.6	1.53	+15	1,598	Fever, restless
Harry G.	56.0	1.60	68.8	73.5	1.40	+21	1,746	Fever, restless
Joseph D.	61.3	1.75	67.4	64.9	1.74	— 3	1,558	Basal
Anna H.	51.0	1.55	62.0	72.0	1.41	+28	1,728	Fever, coughing
Mich. C.	59.0	1.74	68.7	81.5	1.62	+27	1,956	Fever, coughing
John H.	64.5	1.78	70.3	69.9	1.53	+15	1,678	Basal, febrile
				63.0	1.53	+ 5	1,512	Basal, afebrile
Wm. H.	61.0	1.67	66.0	65.6	1.54	+ 9	}	Basal, 38 C.
				72.7	1.53	+21	1,658	Coughing, 38.6 C.
John S.	76.0	2.04	80.6	84.6	1.88	+14	2,030	Basal
Geo. M.	62.3	1.69	66.8	77.6	1.53	+28	1,852	Fever, restless
Joseph R.	82.0	1.98	78.4	70.7	1.74	+ 3	1,697	Basal
J. D.	....	....	....	61.8	1.50	+ 4	1,483	H. G. Barbour's case
G. G.	....	....	....	62.4	1.54	+ 3	1,598	Same
S. L.	....	. ..	....	67.2	1.63	+ 4	1,613	Same

* Average of two operations.

During periods of acute activity of the disease it may be well to limit the protein intake and the total calories fed to patients to the minimum necessary to maintain nitrogen equilibrium without regard to the weight of the patient. Later, when acute symptoms have subsided, and when there is evidence that the natural barriers against the disease are established, a more liberal diet could be given with less fear of the effects of an increased respiratory activity.

An excellent article has just appeared, by Janney and Newell,[32] on the relationship of tuberculosis and diabetes. These authors point out that the course of pulmonary tuberculosis, complicating

32. Janney, N. W., and Newell, R. R.: Treatment of Diabetes Complicated by Pulmonary Tuberculosis, J. A. M. A. **75**:153 (July 17) 1920.

diabetes, does not seem to be influenced unfavorably by the state of undernutrition resulting from a rigid adherence to the proper diabetic diets, but quite the reverse. They show that among diabetic patients the mortality rate from tuberculosis has diminished markedly since the inauguration of the Allen treatment. Similar experience has also been recorded by Joslin.[33] In their own series of cases the development of tuberculosis seems always to have commenced during periods in which diabetic patients were living on a liberal and uncontrolled dietary. In view of these facts no unfavorable results are to be expected from temporary dietary restrictions in nondiabetic tuberculous patients.

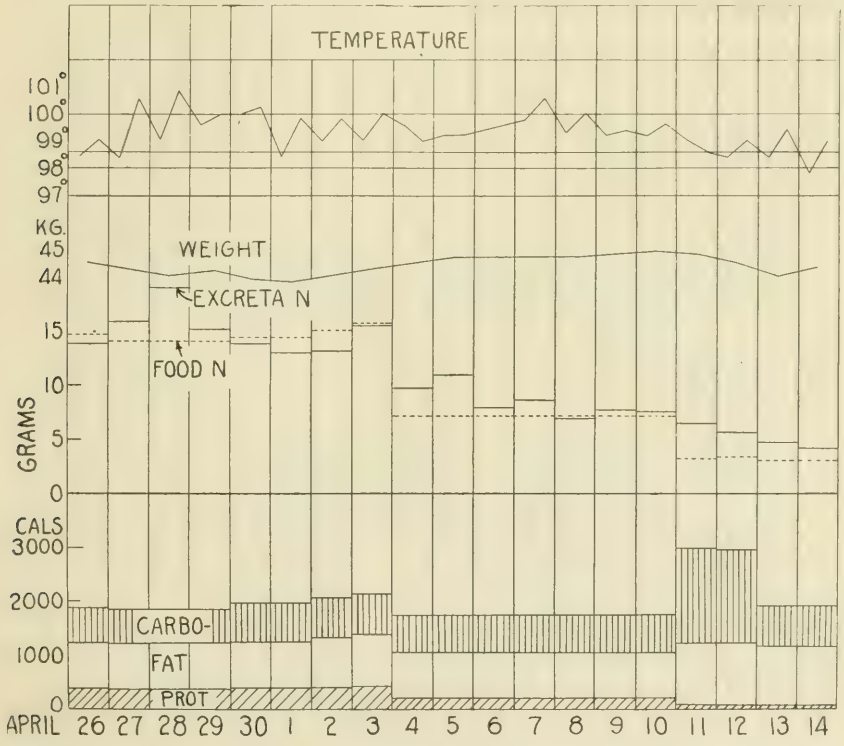

Fig. 18.—Diet chart and nitrogen balance, John H.

In Table 8 estimates of the daily heat production of patients in this series are given. These range from 1,500 to 2,000 calories per day for rest in bed and the fasting state. During periods of activity of a pulmonary tuberculosis the diet need not contain more than 500 calories above the basal requirement (from 2,000 to 2,500 calories), nor more than 60 gm. of protein. The object of such a diet is to maintain the respiratory activity at the lowest level compatible with

33. Joslin: The Treatment of Diabetes Mellitus, 1916.

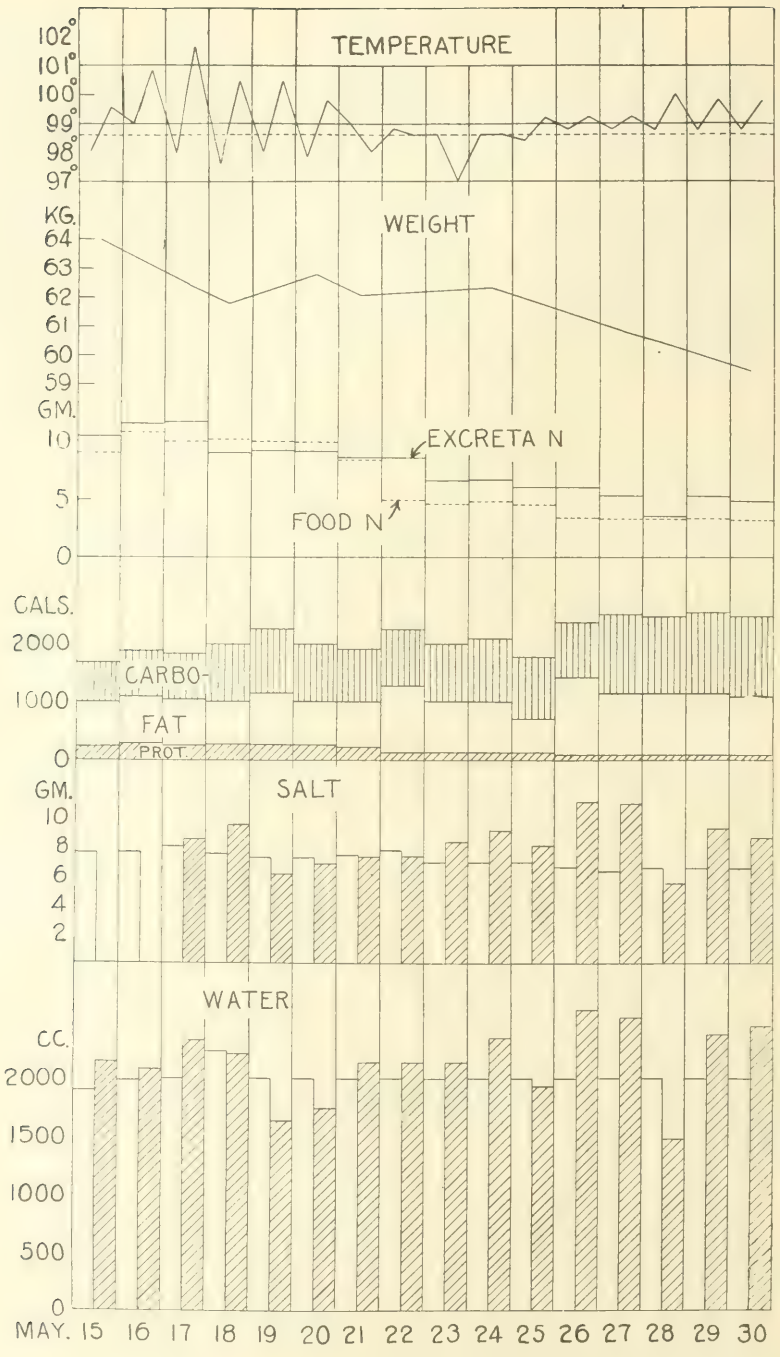

Fig. 19.—Diet chart and nitrogen balance, Joseph R. Water formed by combustion and that eliminated from skin and lungs was not included in the measurement of water balance. Water and salt output in shaded columns. Intake unshaded.

the maintenance of nitrogen equilibrium. To achieve this purpose it is just as necessary not to overfeed as it is to maintain muscular rest.

When the activity of the disease has subsided the total calories in the diet should be raised to meet the requirements of the patient as his muscular activity increases. The protein intake could also be increased to enlarge the repair quota.

SUMMARY

1. The basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. Thus, in ten cases, the variation from average normal was from minus 3 to plus 15 per cent.

2. Further increases in metabolism occur with a rise of body temperature. These increases are not large. Thus one case was given in which the temperature rose 1 degree C. during two hours without a chill. The heat production of the second hour was only two calories greater than that of the first hour. With a rectal temperature of 104 F., (40 C.) the metabolism may be 30 per cent. above the average normal.

3. The basal heat production in tuberculosis may be less than the normal for the same patient when in health; in other words, the loss in weight may be accompanied by a reduction in metabolism which more than compensates for the tendency to increase caused by the disease.

4. Limited data regarding the nitrogen excretion show that, while a toxic destruction of protein does exist in tuberculosis, it is not large. The urinary nitrogen may be reduced to from 5 to 6 gm. per diem, though nitrogen balance may be attained only at a higher level (about 10 gm. a day).

5. The specific dynamic rise in metabolism produced in two cases by the ingestion of a protein meal corresponded closely with that produced by the same meal in three normal men.

CONCLUSIONS

In view of the fact that the food requirements of tuberculous patients are not large, either as regards total energy value or nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as in normals it may be well to limit the protein intake during periods of activity (of the disease) in order to put the lungs at rest.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

I. The Low Alveolar Carbon Dioxide of Cardiac Dyspnea

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It has been shown by many observers, working with various methods, Beddard and Pembrey (1), Porges, Leimdoerfer and Markovici (2), Peabody (3), Pearce (4)—that the alveolar carbon dioxide tension is usually found to be low in cardiac dyspnea. The causes and meaning of this phenomenon have never been clear. In cardiac dyspnea, in contradistinction to most conditions that are associated with a low alveolar CO_2, no proportionate reduction of the alkaline reserve of the blood has been found.

In 1917 one of us (5) studied the relation of the carbon dioxide tension of alveolar air to the bicarbonate concentration of venous plasma. A low alveolar CO_2-tension did not prove to be a constant characteristic of cardiac dyspnea. The alveolar CO_2 was sometimes normal. But it was always lower than normal in relation to the alkaline reserve of the blood as determined by the Van Slyke method. Van Slyke (6) found that in normal subjects the alveolar CO_2-tension maintained a fairly constant relation to the plasma bicarbonate. If the milligrams of CO_2 chemically bound in 1 cc. of plasma is multiplied by the constant 35, the result will be found to agree with the alveolar CO_2-tension (Haldane) expressed in mm. Hg. with about a 10 per cent variation. That is:

$$\text{(Alveolar } CO_2 \text{ in mm. Hg.)} \div \text{(mgm. } CO_2 \text{ chemically bound by 1 cc. of plasma} \times 35) = 100 \pm 10.$$

This observation we corroborated. That such a ratio should obtain in normal resting subjects seems reasonable. To a certain extent it

must represent the $H_2CO_3/NaHCO_3$ ratio, if the alveolar CO_2 can be assumed to be a measure of the arterial CO_2-tension and the bicarbonates of venous plasma an indication of the bicarbonates of whole blood.

In most normal resting subjects such assumptions will give rise to no serious errors. The difference between the carbon dioxide content of the arterial and the venous blood is not large and is comparatively constant. In pathological conditions which interfere with the general circulation or the ventilation of the blood in the lungs, a disturbance of these factors and consequently of the ratio may be expected.

In normal resting subjects the alveolar CO_2/plasma bicarbonate ratio varied between 0.90 and 1.10. In cardiac decompensation with dyspnea and in some very advanced pulmonary conditions we obtained ratios consistently below 0.85. To draw any definite conclusions as to the cause of the phenomenon was impossible. We suggested that it might be an expression of some defect of the normal mechanism for the elimination of carbon dioxide and pointed out the possibility of connecting this with the pulmonary changes which had been demonstrated by Siebeck (7), Peabody (8) and others.

Before any interpretation of the low alveolar CO_2[1] of cardiac decompensation is attempted it is obviously necessary to ascertain whether the method employed is applicable and whether the results obtained can be said to represent the true alveolar tension. The preliminary work was done with the Fridericia pipette (9). This has given rise to some criticism. Repetition with a more orthodox Haldane method has given substantially the same results. Although Pearce (4) has criticised the use of the Haldane method, observations by his own method are substantially in agreement with ours.

Siebeck (7), after a careful study of the respiratory mechanism in cardiac insufficiency, came to the conclusion that all determinations of the alveolar CO_2 were useless in this condition. According to Siebeck (7) the alveolar aeration in cardiac dyspnea is very imperfect, in consequence of which the expiratory air contains an excess of unchanged inspiratory air. Apparently he means that attempts to deduce the arterial CO_2-tension from the values obtained by the Haldane alveolar method are unwarranted. But it is perfectly possible to

[1] Although the reduction of the alveolar CO_2-tension is not absolutely constant, few patients fail to show it. In these few the carbon dioxide capacity of the plasma is distinctly high, while in most instances it is at or slightly below the normal level. It seems proper and simpler, for this reason, to speak of the low alveolar CO_2 of cardiac dyspnea.

consider the alveolar CO_2 on its own merits as a functional entity without any deductions about arterial CO_2-tension. However well grounded the anatomical conceptions of Haldane with regard to the origin of the alveolar air in the normal lung may be, it is quite conceivable that in pathological or physiological disturbances, conditions may be so altered that any anatomical term loses its original significance. Here a functional conception proves of greater value.

A normal expiration may be divided into two parts. The first part is practically useless from the standpoint of respiration; it merely serves to empty the dead space (the nose, mouth, pharynx, larynx, trachea and bronchi) of the room air with which it was filled by the last inspiration. In normal resting subjects the volume of this dead space is fairly constant, varying about an average of 130 cc. Behind this lies a mass of air of nearly constant gaseous composition throughout its whole extent and in close contact with the blood in the pulmonary circulation. This is the air which serves for the effective exchange of gases between the blood and the outside air, and it is a sample of this air that the Haldane method attempts to obtain.

The first object of these studies was to find out whether samples obtained by the Haldane method represented the effective respiratory air. We have employed other methods in order to determine whether they give results in agreement with the Haldane values.

Our studies have been confined to three methods: the Haldane (10), the Plesch (11) and the Henderson (12) venous CO_2. Pearce's (13) method has been omitted because its use in severe dyspnea presents considerable difficulties and also because it demands an amount of apparatus that renders it less adaptable as an ordinary clinical procedure.

THE HALDANE METHOD

The Haldane technique for obtaining alveolar specimens, although criticised for various reasons, is still considered the standard technique for the determination of the arterial CO_2-tension in normal subjects. It has not been generally adopted for clinical studies because of a popular opinion that it is difficult or impossible to obtain good samples in any but highly trained subjects. This we have not found to be the case. We are inclined to believe the observer needs more training than the subject.

In these studies we have adhered in all essential respects to the orthodox Haldane technique, introducing only slight modifications

which tend to diminish subjective errors. One of these is by no means original and consists of the introduction of a three-way brass stop-cock designed by Mr. G. F. Soderstrom and shown in figure 1. This makes it unnecessary for the patient to close the tube with his tongue. Furthermore, no attempt has been made to collect inspiratory and expiratory specimens, as Haldane advises. Instead, samples have been obtained from the end of a forced expiration begun as soon as possible after the completion of a normal inspiration. When the respirations

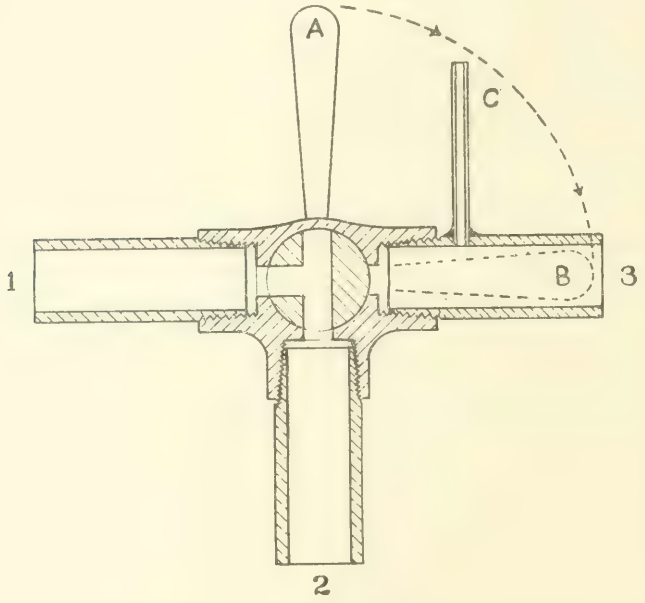

Fig. 1. Three-way stop-cock. *1*, tube for attachment of mouth-piece; *2*, tube leading to spirometer or left open to outside air; *3*, tube for attachment of Haldane tube, with side-arm *C*, to connect with gas sampling tube.

are rapid, as they are in cardiac dyspnea, it is almost impossible to turn the valve at the proper moment to differentiate inspiratory and expiratory alveolar air with any degree of certainty. The propriety of using an expiratory specimen also seems questionable. The prolongation of expiration during dyspnea may be equivalent to holding the breath for the duration of an extra respiration. We have tried to make the subjects force the air out rapidly enough so that the expiration is not considerably longer than a normal one. The specimens as obtained by this method are not all from expirations initiated at the same

point in the respiratory cycle, but at various points in the expiratory phase between full inflation and deflation of the lungs.

In detail the procedure is as follows: The rubber mouth-piece with the stop-cock and tube in place is first put in the patient's mouth with the stop-cock open to the air. He is encouraged to breathe through it to convince him that it will not "shut off his breath." After he has gained sufficient confidence the tube is removed from his mouth and a simple spring nose-clip applied to his nose. When he is sure he can breathe through his mouth alone without difficulty the mouth-piece is replaced in his mouth. He is then instructed how to deliver a sample on command and without altering his normal respirations. The sampling tube is then attached to the side-arm of the stop-cock. The operator stands at the right of the bed supporting the tube with his left hand, with his right on the handle of the stop-cock. When he feels that the breathing is normal and regular he tries to accustom himself to its rhythm, so that he may give the signal at the right moment. The signal is given and the stop-cock turned at the same moment. At the end of the forced expiration the cock is turned to the outside air again before the subject has had time to gasp for breath. The operator soon learns to know whether there has been a subjective error in the technique on his own part or that of the patient.

From an inexperienced subject we are accustomed to take several specimens. Although some of the first will occasionally be obviously too low, it is generally possible to get good agreement on the third or fourth attempt in even the most obtuse subject, as may be seen in tables 1 and 2. In a total of 48 observations on 25 patients, involving the collection and analysis of 127 samples, all but four patients gave duplicate samples that varied by 0.4 per cent or less, an accuracy that compares favorably with that found in trained subjects. Patients with cardiac dyspnea proved no exception to this rule. Three of the four patients (A. R., J. J. F. and D. W.) who gave unsatisfactory results on the basis of this criterion, exhibited Cheyne-Stokes breathing. The fourth (P. O. S.) was very ill, somewhat irrational and showed a slight respiratory irregularity.

The results obtained by the Haldane method are in accordance with those previously obtained with the Fridericia tube. The values are comparatively low and much lower than should be expected from the level of plasma bicarbonates. Two obvious criticisms of the method might be made:

1. That the volume of the expiration is too small to clear the patient's dead space.

TABLE 1

Variations in duplicate Haldane specimens in subjects without respiratory or cardiac disorders

SUBJECT AND CONDITION	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION*	AVERAGE ALVEOLAR CO_2
	per cent			*mm.*
D. P. B., normal	6.16 5.94	0.22	0.22	43.1
	5.25 5.31	0.06	0.06	37.4
	5.72 5.74	0.02	0.02	40.6
	5.39 5.26	0.13	0.13	37.9
	5.16 5.40	0.24	0.24	37.6
	5.39 5.57	0.18	0.18	39.0
	5.60 5.60	0.00	0.00	38.7
	5.39 5.60	0.21	0.21	39.2
	5.45 5.50	0.05	0.05	38.8
	5.62 5.51	0.11	0.11	39.1
	5.32 5.24 5.58	0.34	0.34	38.6
J. P., normal	(5.28) 5.64 5.74 5.45	0.46	0.29	39.9
	5.94 5.85	0.09	0.09	41.6

TABLE 1—*Concluded*

SUBJECT AND CONDITION	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION*	AVERAGE ALVEOLAR CO_2
	per cent			*mm.*
J. P., normal	5.88	0.26	0.26	40.5
	5.62			
	5.35	0.15	0.15	37.5
	5.20			
Capt., normal	6.24	0.07	0.07	44.4
	6.31			
W. S. M., normal	4.70	0.12	0.12	34.8
	4.82			
P. K., gastric neurosis	5.88	0.25	0.25	41.2
	5.61			
	5.86			
Jno. K., diabetes mellitus	4.24	0.16	0.16	30.1
	4.19			
	4.35			
	4.07	0.05	0.05	28.4
	4.06			
	4.02			
C. P., pernicious anemia	3.98	0.11	0.11	28.2
	3.91			
	4.02			
H. R., polycythemia	4.94	0.32	0.32	34.7
	5.11			
	4.79			

* Values in parenthesis in this and the following table have been discarded for the most part on the basis of internal evidence, only.

2. That the low values are produced by subjective errors; preliminary forced inspirations or gasping at the end of expiration.

To rule these out we attached the Haldane tube to a Tissot spirometer which was equipped with a calibrated recording device which will be described later. By this means we were enabled to obtain a graphic record of the respiration during the entire time that the stopcock was turned, and could at the same time measure the volume of the

TABLE 2

Variations in duplicate Haldane specimens with values for alveolar CO_2 and plasma bicarbonates in patients with cardiac disease

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm.*	*mm.*	
J. W., cardionephritic	4.71 4.75 4.76	0.05	0.05	34.6	39.7	5.1	Hypertension. No dyspnea, hyperpnea nor other signs of decompensation
J. A., cardionephritic	(5.21) 6.01 5.76 5.99	0.80	0.25	42.3	49.7	7.4	Hypertension, no dyspnea, cyanosis nor other signs of decompensation at rest
	4.38 3.98 4.25	0.40	0.40	30.0	41.5	11.5	Slight dyspnea and cyanosis. Lungs show râles at right base
A. J., shell shock	4.59 4.43 (4.03)	0.56	0.16	32.5	46.8	14.3	Effort syndrome. No organic cardiac nor pulmonary condition. Discrepancy probably due to over-ventilation
	4.86 4.78	0.08	0.08	33.6			

J. M. L., chronic cardiac	5.43	0.04	0.04	38.5			No symptoms nor signs of decompensation. Lungs clear
	5.39						
	5.11	0.24	0.24	37.2			
	5.35						
A. R., cardionephritic	3.96	0.82	0.82	30.6	31.9	1.3	Hypertension, signs of chronic uremia. Variations in alveolar samples probably due to Cheyne-Stokes breathing
	4.23						
	4.78						
	4.21						
R. W., chronic cardiac	5.69	0.23	0.23	41.0			No dyspnea, cyanosis nor other signs of decompensation
	5.90						
	5.67						
	5.78						
	5.79	0.33	0.33	42.4			
	6.12						
	6.10	0.42	0.42	44.7			
	6.22						
	6.52						
J. C., chronic cardiac	4.65	0.26	0.26	32.0			No dyspnea, cyanosis nor other signs of decompensation while at rest. The low alveolar values obtained in the first observation probably due to overventilation
	4.43						
	4.39						
	5.09	0.29	0.29	38.5	43.9	5.4	
	5.33						
	5.37						
	5.38						

TABLE 2—*Continued*

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm*	*mm.*	
J. J. F., chronic cardiac	4.62 5.08 5.12 4.43	0.69	0.69	34.2	45.5	11.3	
D. W., cardionephritic	(3.08) 4.07 (3.22) 3.59	0.99	0.48	27.3	30.2	2.9	Aortic regurgitation with hypertension. Dyspnea and orthopnea with Cheyne-Stokes breathing. Slightly irrational. Great variations largely due to inadequate coöperation. Low values eliminated by graphic records. Dyspnea probably due to acidosis and not to cardiac disease
P. O. S., chronic cardiac	5.85 5.06 5.27 5.53	0.79	0.79	40.1	52.3	12.2	Extreme decompensation, dyspnea, orthopnea, and Cheyne-Stokes breathing
J. B., chronic cardiac	4.55 4.45	0.10	0.10	32.1	44.8	12.7	Moderate hyperpnea, some cyanosis. Slight edema. Lungs clear. No subjective dyspnea
	4.04 4.18	0.14	0.14	29.3			
	4.21 4.01	0.20	0.20	29.3			

W. W., cardionephritic	3.84 4.15	0.31	0.31	28.5		Moderate dyspnea and orthopnea while at rest. Some signs of fluid in right pleural cavity. Râles over base of left lung
	4.08 4.00 3.97 3.98	0.11	0.11	28.6	43.7	15.1
J. D. B., chronic cardiac	3.11 3.55	0.06	0.06	25.4		Considerable dyspnea and hyperpnea and orthopnea. Moderate cyanosis
	3.35 3.69	0.34	0.34	25.3	41.7	16.4
	3.85 3.82 3.90 3.89	0.08	0.08	27.6	46.6	19.0
	4.51 4.62 4.64 4.31	0.30	0.30	32.2		
J. R., chronic cardiac	4.59 4.56 4.64	0.08	0.08	32.8	48.0	15.2 Severe dyspnea, orthopnea, edema, right hydrothorax
C. D., chronic cardiac	5.10 4.89	0.21	0.21	35.9	46.9	11.0 Severe dyspnea and orthopnea, slight cyanosis. Slight dulness at base of right lung
	4.43 4.75 4.53	0.32	0.32	32.5		

TABLE 2—*Concluded*

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm.*	*mm.*	
Jos. C., cardionephritic	5.36 (4.95) 5.53 5.43	0.58	0.17	38.7	47.8	9.1	Hypertension, auricular fibrillation, marked dyspnea and orthopnea. Some cyanosis. Deformity of right chest
	5.97 5.75 6.06	0.31	0.31	42.2	49.7	7.5	
	(5.78) 6.22 6.60 6.31 6.18	0.82	0.42	44.9	52.2	7.3	
S. I., chronic cardiac	4.01 3.65 3.91	0.36	0.36	27.4	47.6	20.2	Extreme dyspnea, orthopnea, cyanosis and edema, right hydrothorax, râles over remainder of lungs
D. O. C., chronic cardiac	4.21 4.12	0.09	0.09	29.7	40.9	11.2	Considerable cyanosis, orthopnea, and dyspnea. Signs of fluid in right pleural cavity
	3.01 3.83	0.22	0.22	26.5			Cyanosis and dyspnea more marked

D. O. C., chronic cardiac	3.61 3.99 3.67	0.38	0.38	26.7			Condition unchanged
	3.70 3.92 (4.43) 3.56	0.87	0.36	26.6	38.2	11.6	Pleural fluid has increased. Dyspnea more marked
	3.97 3.61	0.36	0.36	23.6			Fluid in both pleural cavities
	3.52 3.82 3.70	0.30	0.30	26.2			Condition unchanged
J. M., chronic cardiac	3.52			25.0	40.9	15.9	Extreme cyanosis. Moderate dyspnea, considerable hyperpnea, right hydrothorax
	4.87 5.03	0.16	0.16	34.8	52.0	17.2	No dyspnea, moderate hyperpnea, cyanosis still marked. Hydrothorax diminished
J. K., chronic cardiac	3.26 3.13 3.03 3.03	0.23	0.23	22.0	37.8	15.8	Extreme cyanosis, slight dyspnea, considerable hyperpnea, few râles scattered over both lungs
	4.24 4.86 4.56	0.62	0.62	32.5			Dyspnea gone, cyanosis slight, still some hyperpnea. Lungs clear
C. C., chronic cardiac	3.95 3.68 3.91	0.27	0.27	27.1			Marked cyanosis. Little dyspnea. No orthopnea. Considerable hyperpnea

TABLE 3

Relation of alveolar CO_2 to volume of expiration

SUBJECT	VOLUME OF EXPIRATION	ALVEOLAR CO_2
	cc.	*per cent*
J. C., chronic cardiac compensated	1016	5.09
	823	5.33
	807	5.37
	790	5.38
W W., chronic cardiac decompensated	797	4.08
	864	4.00
	615	3.97
	665	4.35
	385	4.32
R. W., chronic cardiac compensated	710	5.90
	452	5.67
	645	5.78
	758	6.10
	651	6.22
	516	6.52
J. D. B., chronic cardiac decompensated	1081	4.51
	1290	4.62
	758	4.64
	986	4.34
A. R., cardionephritic. Periodic breathing	505	3.96
	535	4.23
	430	4.78
	505	4.21
D. W.,* cardionephritic. Periodic breathing	(758	3.08)
	677	4.07
	(629	3.22)
	952	3.59

* See figure 2.

expiration. Table 3 shows the values obtained from six experiments done in this way. From the first five experiments it is evident that the expiratory volume is sufficient to clear completely any but an enormously increased dead space. If the dead space were increased to this

degree, however, the alveolar CO_2-tension should vary with the expiratory volume. This relation does not obtain. In only one instance, the second observation on R. W., is any such relation even suggested, and in this case the total variation is only 0.23 per cent.

In none of these cases is there any indication in the graphic records of inspiratory activity during the time that the stop-cock was open. That the method is capable of showing such subjective errors is demonstrated in the record of D. W. (fig. 2). This patient presented symptoms of uremia with Cheyne-Stokes respiration. His tracings show that the low values obtained from the first and third samples were due

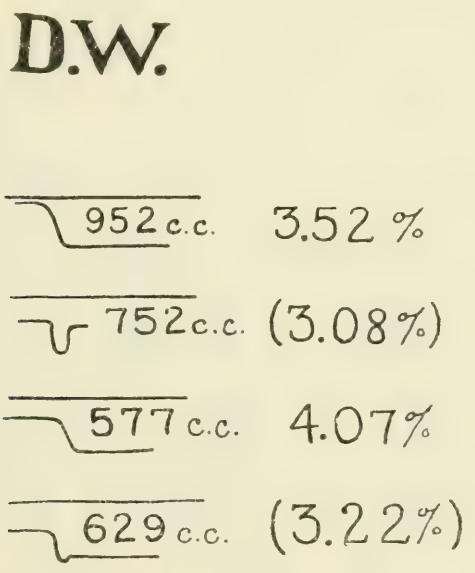

Fig. 2

to inspirations while the valve was open and before the samples had been withdrawn. The discrepancy in the two remaining values seems to depend on the fact that one was obtained during an apneic, the other during a dyspneic period.

The low alveolar CO_2 is not due to subjective errors on the part of the patient nor to any considerable increase in the volume of the dead space.

The alveolar CO_2 after rebreathing. One of the most striking characteristics of decompensated cardiac patients is the intolerance to an increase of CO_2 in the inspired air (14).

It has been shown by Haldane (15) and others that when a person rebreathes air the alveolar CO_2-tension and the ventilation increase as the CO_2 in the inspired air rises. When the alveolar CO_2-tension has risen to a certain point the patient becomes extremely dyspneic and uncomfortable. This we may call the point of intolerance to CO_2. If the alveolar CO_2 be low in cardiac dyspnea at rest it seems reasonable to suppose that it should also be relatively low after rebreathing to the point of intolerance.

For the rebreathing experiments a 100-liter Tissot spirometer, accurately balanced and calibrated at all levels, was employed. To separate the inspired from the expired air a two-way T-valve of the Douglas type was used. Between the mouth piece and this T-valve was interposed the three-way brass stop-cock described above. The opening with the side-arm was, as usual, fitted to a long, wide-bore rubber tube for the collection of alveolar specimens. The other arm was connected with the T-valve. (The total instrumental dead space was about 50 cc.) In this way it was possible to collect specimens of alveolar air during the course of a rebreathing experiment by merely turning the stop-cock during expiration and directing the patient to breathe out forcibly. The inspiratory air was withdrawn from the spirometer through the opening in the top usually employed for the insertion of the thermometer. Samples of the inspiratory air were drawn from this tube near the T-valve through a small rubber side arm. Graphic records of the respirations were obtained by means of a pen attached to the counter-weight of the spirometer. As it moved in a vertical plane only, direct calibration was possible. Simultaneous time records were obtained. The apparatus is represented diagrammatically in figure 3.

The spirometer was filled with 20 liters of room air for each experiment. A larger amount was found to prolong the experiment unduly and to introduce a considerable element of fatigue. Smaller amounts rendered the succession of events too rapid to permit the introduction of all the necessary procedures and accurate analysis of the results obtained.

The minute volume attained in the rebreathing experiments was calculated from the average tidal air and the respiratory rate during the last half-minute of the experiment, except in one or two cases where the limit of tolerance was reached so rapidly that it was necessary to use a shorter terminal period for purposes of calculation. Of course, assuming that the minute volume increases continuously throughout

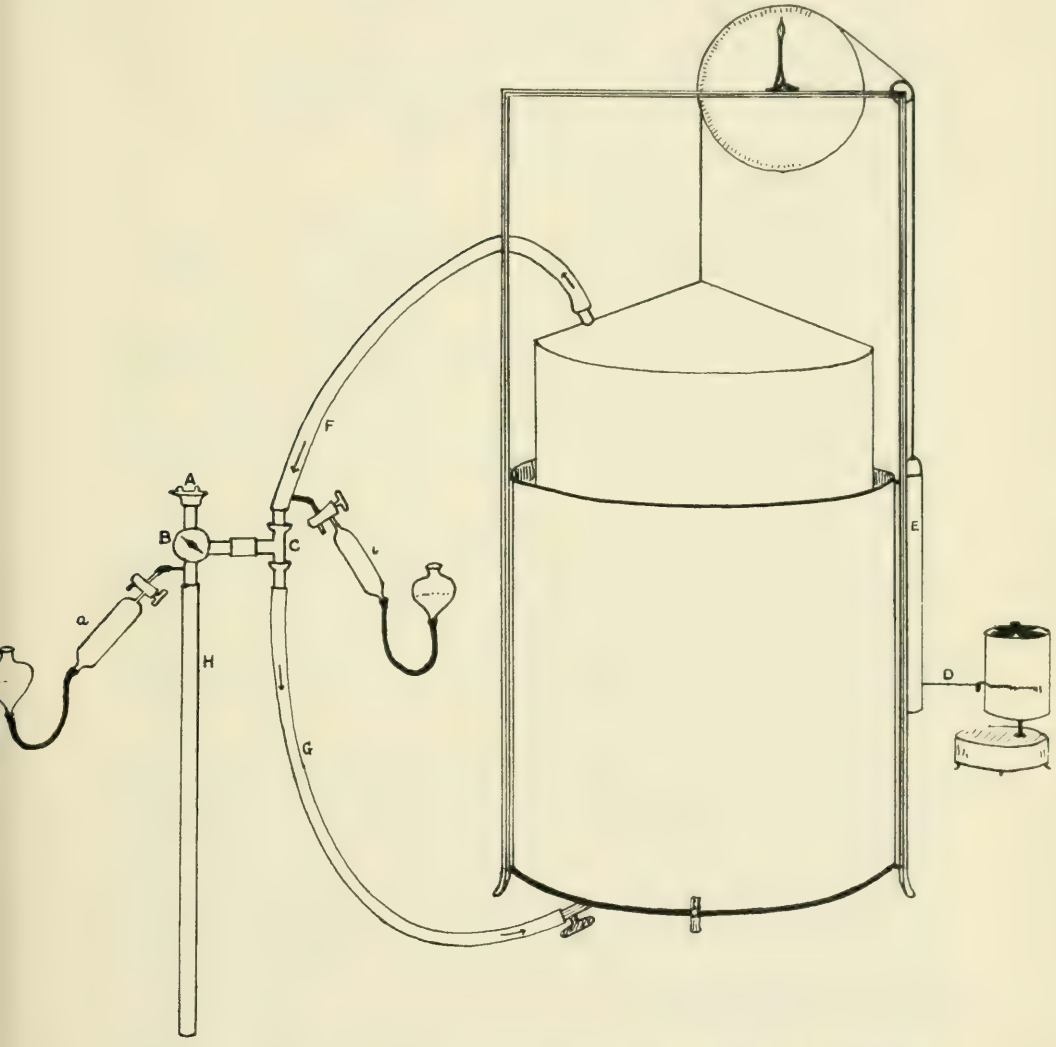

Fig. 3. *A*, mouth-piece; *B*, 3-way stop-cock; *C*, Douglass valve; *F*, inspiratory tube; *G*, expiratory tube; *E*, counterweight of spirometer; *D*, recording pen; *H*, Haldane tube; *a*, sampling tube for alveolar air; *i*, sampling tube for inspiratory air.

the course of the experiment, the values obtained in this way must be somewhat too low. On the other hand, the respirations never become absolutely regular, and calculations based on too small a number will be subject to considerable error. In rebreathing so large a volume as 20 liters the respiratory increase is sufficiently gradual to permit the use of the last half-minute, in the majority of instances, with the introduction of no significant error.

After a satisfactory determination of the resting alveolar CO_2 and minute volume had been made, a rebreathing experiment was begun. The patient was urged to continue as long as he felt able. When he had reached the limit of tolerance the valve of the three-way stop-cock was opened to the Haldane tube during an expiration. The patient was told to breathe out forcibly and the valve was again closed before the following inspiration. The patient was at once disconnected from the apparatus and the alveolar sample removed for analysis. The second operator at the same time removed a sample from the inspiratory tube.

Of course, the coördination and coöperation of the subject were necessary and there were opportunities for mistakes. Altogether eleven successful experiments were made on two normal subjects; one out of two was successful in a patient with a gastric neurosis; one in shell shock; three in two compensated cardiacs; and five out of seven attempted in four patients with cardiac decompensation. The results appear in summarized form in table 4.

A very striking difference is apparent at once between the decompensated cardiac cases and the others. The former were unable to tolerate as much CO_2 in the inspired air and their alveolar CO_2 did not rise to as high a level. This was due to no lack of will power on the part of the cardiacs because in one or two cases they continued rebreathing to the point of exhaustion, while none of the compensated subjects went beyond a state of moderate discomfort. The alveolar CO_2 at the point of intolerance is therefore lower in decompensated cardiacs than it is in normal persons.

With the exception of A. J., the shell shock patient, the height of the alveolar CO_2 at which intolerance was reached bore a general relation to the preliminary alveolar CO_2-tension. In this one case the low resting alveolar CO_2 was due to over-ventilation. This was clearly shown by the fact that his initial reaction to rebreathing was a reduction of the minute-volume, instead of an increase.

TABLE 4

The effect of rebreathing on the alveolar CO_2

NUMBER AND NAME	RESTING ALVEOLAR CO_2	AT END OF REBREATHING EXPERIMENT		DIAGNOSIS AND REMARKS
		Inspiratory air CO_2	Alveolar CO_2	
	per cent	*per cent*	*per cent*	
		8.36	8.52	Normal adult. Continued rebreathing to point of considerable discomfort
	6.05	8.01	8.16	
1. D. P. B.		7.93	8.21	To discomfort
	5.28	8.06	8.30	To discomfort
	5.73	7.84	7.95	To slight discomfort
		6.86	7.53	To slight discomfort
		7.90	8.32	Normal adult. To considerable discomfort
2. J. P.....		7.95	7.98	To extreme discomfort
		6.90	7.27	To discomfort
		6.86	7.05	To considerable discomfort
	5.78	6.61		Gastric neurosis
3. P K.....	5.50	6.07	6.85	To moderate discomfort. No exhaustion
	5.50	5.90	7.30	Chronic cardiac valvular disease, compensated
4. T. deC..	5.70	6.59	7.27	Rebreathed to point of moderate discomfort
5. J. M. L...	5.23	7.54	7.92	Chronic cardiac. Compensated. Continued rebreathing to point of considerable discomfort
	4.51	6.26	6.30	Shell shock with effort syndrome.
6. A. J.....	4.72	6.30	6.89	To moderate discomfort only
	5.92	5.74	6.36	Chronic cardiac, valvular disease,
7. J. A.....		4.52	7.34	compensated while at rest. Rebreathed to point of considerable discomfort with some exhaustion
	4.50	3.70		Chronic cardiac valvular disease.
8. J. B.....	4.50	3.92	5.55	Moderate dyspnea while at rest.
	4.11	5.17	6.26	In the first two experiments continued only to mild discomfort. In the last experiment considerable discomfort. Somewhat exhausted

TABLE 4—*Concluded*

NUMBER AND NAME	RESTING ALVEOLAR CO_2	AT END OF REBREATHING EXPERIMENT		DIAGNOSIS AND REMARKS
		Inspiratory air CO_2	Alveolar CO_2	
	per cent	*per cent*	*per cent*	
9. Jos. C....	5.93	3.88	6.68	Cardio-nephritic with cardiac decompensation. Considerable dyspnea and hyperpnea. Continued to point of considerable discomfort. Somewhat exhausted
10. C. D...	5.00 4.57	2.13 2.89	5.10	Chronic cardiac, valvular disease with marked decompensation. Continued to point of marked exhaustion
11. D. O. C.	4.17	2.94 2.53	5.72	Chronic cardiac, valvular disease with decompensation. Continued rebreathing to point of discomfort with some exhaustion

In cardiac dyspnea, then, the alveolar CO_2 is low at the point of intolerance. The relation of the alveolar CO_2 at this point to the resting alveolar CO_2 is similar to that found in normal persons. This is further evidence that the air in the lungs in cardiac dyspnea really presents a diminished CO_2-tension.

THE PLESCH METHOD

Modifications of the Plesch method of obtaining samples of alveolar air have been employed extensively in cardiac disease and other pathological conditions by numerous workers. Both Porges (2) and Peabody (3) used it for their studies on cardiac dyspnea. With this method, the subject rebreathes a limited volume of air, usually 600 to 1000 cc. a number of times, usually from 5 to 10, in a period of time usually between 20 and 30 seconds, which is supposed to be less than the duration of a single complete circulation of the blood. With normal resting subjects it gives values that lie a little higher than those obtained by the Haldane method and is assumed to represent the tension of CO_2 in the venous blood.

Usually the rate and depth of the respirations and the duration of rebreathing can be varied within rather wide limits with only a slight

variation in the analyses obtained. This might reasonably be expected even if the theoretical basis of the method were entirely wrong. It has been shown that in normal subjects at rest, lung volume, carbon dioxid output, arterial CO_2-tension and venous CO_2-tension vary within narrow limits absolutely and in relation to one another.

The assumption that such an empirical method is equally applicable to the study of a condition in which all these factors are greatly disturbed, is hardly justifiable.

We have made a few observations on normal subjects and on patients with cardiac disease (see table 5) in which we tested the effect of varying

TABLE 5

Results of varying time and number of respirations on Plesch-alveolar CO_2

	NORMALS				J. M. L. COMPENSATED CARDIAC	DECOMPENSATED CARDIACS					
	D. P. B.			J. P.		S. I.	D. O. C.		W. W.	J. B.	
5 respirations in 25 seconds	6.17	6.04	5.24	6.29	6.08	4.48	4.85	5.41	4.70	5.03	4.82
10 respirations in 25 seconds	6.53	5.97	5.90	6.22	6.76	4.62	4.92	5.88	5.41	5.14	5.53
5 respirations in 35 seconds	6.43	6.35	5.89	6.34	6.90			5.99	5.67	5.63	5.81
10 respirations in 35 seconds	6.34	6.41	5.88	6.43	6.92	4.70		6.29	5.99	5.50	
Average value	6.37	6.19	5.73	6.32	6.67	4.60	4.89	5.89	5.44	5.33	5.17
Maximum variation	0.36	0.44	0.66	0.21	0.84	0.22	0.07	0.88	1.29	0.60	0.99
Haldane alveolar CO_2	5.28	5.33		5.61	5.41	3.86	3.72	3.75	4.34	4.11	4.11
Difference between Plesch and Haldane	1.09	0.86		0.71	1.26	0.74	1.17	1.99	1.10	1.22	1.06

the time and rate of rebreathing within certain limits. The time limits chosen were 25 and 35 seconds; the number of breaths 5 and 10. The apparatus used was essentially the same as that recommended by Peabody (16): a three-way brass stop-cock described above, which connected the subject either with the outside air or a rebreathing bag containing 1000 cc. of room air. The bore of the valve and tubing was 1.75 cm., the instrumental dead space, including the rubber mouthpiece, 30 cc. Rebreathing was always begun after a forced expiration and the patient was directed to make a maximum respiratory effort with each breath.

In the case of J. P. the total difference obtained within the limits of variation of time and number of respirations employed was 0.21 per cent. In D. P. B. the differences were greater: from 0.36 to 0.66 per cent. Moreover, in one experiment on the latter (no. III) it appears that the duration of the experiment has less influence than the number of respirations. In the cardiac patients studied the differences were slightly larger, in one case 1.29 per cent. Again variations in the number of respirations appear almost as important as variations in time. One would be rather at a loss to know which values to accept under these conditions.

Of course 35 seconds and 10 breaths are both in excess of the limits usually employed. The objection may be raised that we have not limited the element of time and the number of breaths sufficiently. To us it seems essential to determine whether limitation of experimental factors produces an equivalent limitation of variation in all subjects. One is not justified in producing an apparent constancy in results by an arbitrary limitation of experimental variations.

THE HENDERSON-LAURENS METHOD

Y. Henderson (12) has recently published a method for the determination of the venous CO_2-tension. It does not differ in principle from previous methods, but demands less effort and intelligence on the part of the subject and is therefore more applicable to clinical studies. It depends on the principle of intermittent rebreathing. Laurens (17) has pointed out that it is necessary to regard certain precautions in rebreathing because diffusion of CO_2 is more perfect during respiratory motions than it is while the chest is motionless. Our technic has been modified, therefore, to meet his requirements.

The apparatus used was the same as that employed in the Plesch studies. The rebreathing bag was filled with about 2000 cc. of expiratory air. In most cases a second observation was made in which the bag was filled with a mixture of air with 6.5 to 10 per cent CO_2. While the patient was breathing room air quietly through the valve, he was ordered to give a maximum expiration. When his lungs were completely deflated the stop-cock was turned. He then filled his lungs with a mixture from the bag by a deep inspiration, retained the air in his lungs about 10 seconds and expired into the bag forcibly. The stop-cock was then turned to the room again and he resumed normal respirations. After a sufficient interval to permit the respirations to return

to normal the same procedure was repeated. After each respiration the mixture in the bag was tested for CO_2. The rebreathing was continued until analyses after successive respirations showed that the CO_2-tension had reached a practically constant level. In normal subjects this level is reached after about 7 rebreathings and the level attained in rebreathing expired air and CO_2 rich mixtures is the same.

The results of these studies are shown in table 6. Not all of the experiments are entirely satisfactory; but a more or less constant level is reached in cardiac subjects as well as in normals.

There is a surprisingly close agreement between the venous alveolar values obtained by the Henderson-Laurens method and the average of the values obtained by the Plesch method. The application of the Plesch method, in the simple form usually employed, to the physiologic study of cardiac disease, seems hardly warranted. The limitation of the number of respirations and the duration of rebreathing is more or less arbitrary and based on the study of normal subjects only. The use of an average value obtained from a series of observations in which both time and number of respirations has been varied seems preferable. In normal and cardiac subjects values so obtained agree with those obtained by at least one other venous method.

The difference between the Henderson and the Haldane alveolar CO_2 is greater in subjects with cardiac dyspnea than in normal persons or cardiac patients without dyspnea. In spite of this the actual values found by the Henderson method in cardiac dyspnea are slightly lower than normal. This is again evidence that the carbon dioxide tension of the air in the lungs is reduced in cardiac dyspnea.

It is not possible to argue that the difference between the Henderson and the Haldane alveolar CO_2 represents the difference of CO_2-tension between arterial and venous blood. The Haldane values can not be interpreted as a measure of the arterial CO_2-tension until the criticisms of Siebeck have been answered. The only way to answer them is by the direct determination of the arterial CO_2-tension. The objections to the application of alveolar methods to the determination of the carbon dioxid tension of venous blood are even greater. Christiansen, Douglas and Haldane (18) have pointed out that direct determination of the venous carbon dioxid tension by these methods is impossible. The peculiar effect of oxygen on the carbon dioxid dissociation curve of the blood necessitates the introduction of a correction for the oxygen unsaturation of venous blood. An average correction can be applied in the case of normal persons without any considerable error. In

TABLE 6

Comparison of Henderson-Lawrens with Haldane method and its application to cardiac dyspnea

SUBJECT AND CONDITION	REBREATHING EXPIRED AIR		REBREATHING CO_2-AIR MIXTURE			CALCULATED VENOUS ALVEOLAR CO_2	PLESCH ALVEOLAR CO_2	HALDANE ALVEOLAR CO_2	DIFFERENCE BETWEEN HENDERSON AND HALDANE	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE
	Number of rebreathings	CO_2 found in bag	Mixture rebreathed CO_2	Number of rebreathings	CO_2 found in bag					
		per cent	*per cent*		*per cent*	*mm.*	*mm.*	*mm.*	*mm.*	*mm.*
D. P. B., normal	2	5.25				44.9	45.8	37.9	6.9	
	3	5.74								
	4	6.17								
	5	6.28								
	4	5.69				45.1	45.4	37.6	7.5	
	5	6.21								
	6	6.26								
	7	6.38								
			6.64	6	5.79	43.4		39.0	4.4	
	7	6.14		7	5.82					
	8	6.07		8	5.86					
	9	6.13		9	6.01					
			7.55	6	5.97	42.7		39.3	3.4	
	7	5.95		7	5.88					
	8	6.23		8	5.93					
	9	6.06								
	7	5.80	10.02	5	5.99	41.9		39.2	2.7	
	8	5.84		6	6.03					
	9	5.79		7	5.91					

	2	6.13				43.8	45.0	39.9	3.9	
	3	6.13								
	5	6.20								
			10.34	3	7.02	48.6				
				4	7.01					
	7	6.67		5	6.93					
	8	6.83		6	6.86					
J. P., normal	9	6.83		7	6.77					
	8	6.14	6.96	5	6.34	44.8				
	9	6.23		6	6.28					
	10	6.21		7	6.34					
			7.14	5	5.99	41.9		42.3	4.0	
	7	5.82		6	5.98					
	8	5.76		7	5.95					
	4	6.45				46.6		42.3	4.3	49.7
J. A., chronic cardiac	5									
compensated	6	6.53								
	7	6.52								
	7	5.59	10.0	7	6.53	44.9		37.7	7.2	
J. C., chronic cardiac compensated	8	5.75		8	6.45					
	9	6.00								
	3	6.25				48.4	47.5	38.5	9.9	
J. M. L., chronic cardiac compensated	4	6.66								
	5	6.74								
			7.64	7	6.44	47.8		42.4	5.4	
R. W., chronic cardiac compensated	8	6.44		8	6.72					
	9	6.52		9	6.72					

TABLE 6—*Concluded*

SUBJECT AND CONDITION	REBREATHING EXPIRED AIR		REBREATHING CO_2-AIR MIXTURE			CALCULATED VENOUS ALVEOLAR CO_2	PLESCH ALVEOLAR CO_2	HALDANE ALVEOLAR CO_2	DIFFERENCE BETWEEN HENDERSON AND HALDANE	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE
	Number of rebreathings	CO_2 found in bag	Mixture rebreathed CO_2	Number of rebreathings	CO_2 found in bag					
		per cent	*per cent*		*per cent*	*mm.*	*mm.*	*mm.*	*mm.*	*mm.*
J. B., chronic cardiac decompensated	2	5.07				38.9	38.4	29.3	9.6	
	3	5.48								
	4	5.43								
	5	5.25								
Jos. C., chronic cardiac decompensated	4	6.11				45.2		38.7	6.5	47.8
	5	6.35								
	6	6.39								
	7	6.30								
	6	6.77	8.92	5	6.99	48.9		44.9	4.0	52.2
	7	6.34		6	7.06					
	8	6.40		7	6.95					
W. W., chronic cardiac decompensated	7	5.64	6.44	7	5.36	38.7		28.6	10.1	43.7
	8	5.45		8	5.33					
	9	5.43		9	5.59					
D. O. C., chronic cardiac decompensated	3	5.29				40.6	42.1	26.7	13.9	38.2
	4	5.71								
	5	5.56								
	6	5.74								
	7	4.89	7.79	7	5.43	36.0		25.3	10.7	
	8	4.92		8	5.15					
	9	5.04		9	5.07					
Averages (normal subjects and compensated cardiacs)						45.0		39.2	5.4	
Averages (decompensated cardiacs)						41.4		32.3	9.1	

patients with cardiac decompensation, however, the oxygen unsaturation of the venous blood is much greater (19) and more variable. The use of a standard correction factor may therefore involve considerable error.

SUMMARY AND CONCLUSIONS

The Haldane method of obtaining alveolar air has been employed in the study of a series of cardiac patients with dyspnea with no greater variation in results than is found in studies of trained normal subjects. The carbon dioxid tension of alveolar air thus obtained has been found consistently low in comparison with the carbon dioxid capacity of venous plasma. The comparatively low values are not due to technical or subjective errors nor to any considerable increase in the volume of the dead space. The patient with cardiac decompensation maintains his alveolar CO_2 at a lower level than does the normal and the level to which he will permit it to rise under the influence of rebreathing is proportionately reduced.

The Plesch method gives variable results according to the number of respirations and the duration of rebreathing. If, however, an average of a series of observations in which these factors have been varied is employed the results agree with those given by the Henderson method for venous alveolar CO_2. The values found by these methods are somewhat lower in decompensated cardiac subjects than in normal persons; but are high in relation to the values given by the Haldane method.

No attempt has been made to translate alveolar CO_2-tension into terms of arterial or venous CO_2-tension. The alveolar air has been considered entirely from a functional standpoint as that portion of the air in the lungs which is available for the exchange of gases between the blood in the pulmonary circulation and the outside air. If the term "alveolar air" is used in this sense, it may be said that the alveolar CO_2-tension of subjects with cardiac dyspnea is low in comparison with the carbon dioxid capacity of the plasma. As the latter is variable, but seldom abnormally high, the alveolar CO_2-tension is usually not only relatively but absolutely diminished.

BIBLIOGRAPHY

(1) Beddard and Pembrey: Brit. Med. Journ., 1908, ii, 580.
(2) Porges, Leimdoerfer and Markovici: Zeitschr. f. klin. Med., 1913, lxxvi, 446.
(3) Peabody: Arch. Int. Med., 1916, xvi, 846.

(4) Pearce: Journ. Lab. Clin. Med., 1917, ii, no. 12.
(5) Peters: This Journal, 1917, xliii, 113.
(6) Van Slyke, Stillman and Cullen: Journ. Biol. Chem., 1917, xxx, 401.
(7) Siebeck: Deutsch. Arch. f. klin. Med., 1912, cvii, 253.
(8) McClure and Peabody: Journ. Amer. Med. Assoc., 1917, lxix, 1954.
(9) Fridericia: Berl. klin. Wochenschr., 1914, li, 1268.
(10) Haldane and Priestley: Journ. Physiol., 1905, xxxii, 225.
(11) Plesch: Zeitschr. f. exper. Pathol. u. Therap., 1909, iii, 380.
(12) Henderson: Journ. Biol. Chem., 1917, xxxii, 325.
(13) Pearce: This Journal, 1917, xliii, 73.
(14) Peabody: Arch. Int. Med., 1917, xx, 433.
(15) Campbell, Douglas, Haldane and Hobson: Journ. Physiol., 1914, xliii, 303.
(16) Peabody: Arch. Int. Med., 1914, xiii, 497.
(17) Laurens: This Journal, 1918, xlvi, 147.
(18) Christiansen, Douglas and Haldane: Journ. Physiol., 1914, xlviii, 244.
(19) Lundsgaard: Journ. Exper. Med., 1918, xxvii, 219.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

II. A Note on the Effective Lung Volume in Cardiac Dyspnea

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That the vital capacity of the lungs is reduced during cardiac decompensation is a well-established fact (1), (2). A few experiments have been conducted to find out whether this reduction is associated with a change in the total air containing space of the lungs and to ascertain the effect of such a change on the functional efficiency of the respiratory mechanism.

METHODS

The problem has been approached in two distinct ways: *a*, by the application of the Lundsgaard (3) method for measuring the lung volume by rebreathing oxygen; *b*, by a study of the effect of continuous rebreathing of air on the volume of the tidal air and the comparison of the latter with the vital capacity.

The lung volume of a few normal and pathological cases was measured by the Lundsgaard (3) method of rebreathing oxygen. A graphic record of the preliminary respirations and the vital capacity was obtained with a Tissot spirometer by means of a combination of valves similar to that used for rebreathing experiments and described in the preceding paper (4). A rebreathing bag containing a measured amount of oxygen was attached in place of the Haldane tube. In all cases the subject commenced rebreathing from the position of complete expiration. The volume of the residual air was calculated from the gas mixture in the bag at the end of the observation. The volume of the vital capacity was obtained from the graphic record. The values thus obtained were compared with those obtained by the Lundsgaard (3) method of chest measurement.

TABLE I

Vital capacity and lung volume

NAME AND CONDITION	DATE	VITAL* CAPACITY	RESIDUAL AIR*	LUNG† VOLUME	METHOD OF DETERMINATION: Volume of O_2 re-breathed	METHOD OF DETERMINATION: Number of respirations	METHOD OF DETERMINATION: Time of rebreathing	REMARKS
		cc.	*cc.*	*cc.*	*cc.*		*seconds*	
1. D. P. B., normal	*Lundsgaard measurements*	*3332*‡†	*1478**†	*4810**†				Low Lundsgaard measurement probably faulty and due entirely to excessively short sternum
	v/19	4429	1662	6091†	3000	7	18	
	v/21	4328	1551	5879†	3000	7	15	Ratio V. C./Surface Area = 2.73
	v/22	4239	1715	5954†	2050	7	17	
		4284	1632	5916†	2010	7	15	
2. J. P., normal	*Lundsgaard measurements*	*3704*	*1609*	*5313*				
	v/22	3772	1621	5393	3000	7	17	
		3876	1723	5599	2000	7	17	
3. J. C., chronic cardiac	*Lundsgaard measurements*	*2980*	*1460*	*4390*				Young boy of 18 with early rheumatic endocarditis Compensated at rest
	vi 10/19	2345	1560	3905	2070	7	18	No dyspnea nor hyperpnea at rest. Lungs clear
		2432	1515	3947	2070	7	18	

	Lundsgaard measurements	*2930*	*1460*	*4390*				Chronic cardio-nephritic. Hypertension. Cardiac hypertrophy. Blood pressure 210
4. J. A., chronic cardiac	v 16/19.....	2430						No dyspnea nor hyperpnea while at rest. Lungs clear
	vi 7/19.....	1242	1214	2456	2020	7	19	Some hyperpnea even when at rest in bed. Lungs clear except showers of râles at right base
		1329	1250	2579	1500	7	17	
		1418						
	Lundsgaard measurements	*3640*	*1740*	*5380*				At time of examination was found to have very little hyperpnea. Also had a reduction of the plasma bicarbonate. The hyperpnea was probably due to the reduction of the alkaline reserve and not to cardiac factors. Chest clear. Periodic breathing
5. A. R., chronic cardiac	vi 27/19.....	1489	1744	3233	1510	7	17	
		1789						
	Lundsgaard measurements	*4698*	*2315*	*7013*				Moderate hyperpnea. Some dulness and râles at extreme bases on both sides
6. W. W., chronic cardiac	vi 24/19.....	1174	2320	3494	1500	7	14	
	vi 25/19.....	1452	2190	3642	1535	7	20	

TABLE 1.—*Concluded*

NAME AND CONDITION	DATE	VITAL* CAPACITY	RESIDUAL AIR*	LUNG* VOLUME	METHOD OF DETERMINATION: Volume of O_2 rebreathed	METHOD OF DETERMINATION: Number of respirations	METHOD OF DETERMINATION: Time of rebreathing	REMARKS
		cc.	*cc.*	*cc.*	*cc.*		*seconds*	
7. R. W. chronic cardiac	*Lundsgaard measurements*	*3930*	*1870*	*5800*				No dyspnea when at rest. Some impairment of resonance at extreme right base
	vi 23 19	1714	1264	2978	2050	7	17	
		1064	1244	2308	2000	7	17	
	vi 24 19	1869						
	vi 30 19	2080	1091	3171	2040	7	17	
	Lundsgaard measurements	*3540*	*1800*	*5340*				
	iv 29 19	1303						Marked dyspnea when at rest. Some signs of fluid at right base
S. D. O. C., chronic cardiac	vi 2 19	920	757	1677	2020	7	Very rapid	Some fluid in right chest
		985	799	1784	1040	15	17	
	vi 6 19	1193	873	2066	1060	15	Very rapid	Dyspnea more marked. Fluid to angle of right scapula; 1450 cc. removed just after experiment
	vi 9 19	1068	887	1955	990	12	17	Dyspnea less marked. Fluid above angle of right scapula. Some dulness at extreme left base
		1132	861	1993	1000	15	17	

* In each case the values for the normal lung volume as determined by the Lundsgaard method of chest measurement are reported first, in italics. Below them appear the values obtained by the rebreathing method.

† The great discrepancy between the observed and the calculated lung volumes of DPB seems to be due to a very short sternal measurement. The relation between his vital capacity and surface area is quite normal, 2.73. In the light of the work of Dryer and that of West it appears that the surface area is a better criterion from which to calculate the vital capacity. Unfortunately we have not sufficient data to permit recalculations on this basis.

The apparatus and method employed in the rebreathing experiments were described in the first paper of this series (4). By a study of the tidal air of normal subjects and cardiac patients after the continuous rebreathing of air from a spirometer, we hoped to gain some information on the effect of the reduction of vital capacity on the functional efficiency of the respiratory mechanism.

RESULTS

The results of the lung volume determinations are collected in the first three columns of table 1. In each case the normal lung volume, as calculated by the Lundsgaard (3) method of chest measurement is reported first, in italics. Below it appear the values obtained from the rebreathing experiments. In the fourth, fifth and sixth columns are given the conditions of the experiments: the volume of oxygen taken in the rebreathing bag; the number of respirations and the duration of the rebreathing.

The first two subjects were normal. The third had chronic cardiac valvular disease without decompensation. His vital capacity, residual air and lung volume were almost normal. Number 4, at the first observation, in the absence of dyspnea, showed only a slight reduction of the vital capacity. Three weeks later, with a recurrence of dyspnea, his vital capacity was found to be only half as large. His residual air was not far from normal. Unfortunately his residual air was not determined at the time of the first observation.

Number 5, A. R., had hypertensive nephritis with some edema and signs of uremia: drowsiness and Cheyne-Stokes breathing. He showed no considerable hyperpnea, although his plasma bicarbonate was reduced. His chest was entirely clear. His vital capacity was very small but his residual air practically normal.

The last three were decompensated patients with dyspnea and showed very low vital capacities. The volume of the residual air was also considerably below normal in the last two. With the exception of the last patient, who had a massive hydrothorax, the physical signs found in the chest were insignificant in comparison with the diminution of lung volume.

These results indicate that, in patients with cardiac dyspnea, the total volume of air in the lungs which can be detected by the usual methods is considerably less than that found in normal persons. The largest part of the reduction in lung volume is due to a diminution of the vital capacity. The residual air is unchanged or slightly reduced.

The results of the rebreathing experiments are given in table 2. The subjects are arranged from above downward according to the magnitude of their vital capacities, which appear in column 1. In column 2 is given the normal vital capacity as calculated from the Lundsgaard (3) chest measurements. In column 3 is shown the average resting tidal air and in column 4 the tidal air at the end of a rebreathing experiment. The last we have called the "maximum tidal air" because it is the largest respiratory volume which the subject will exchange under the influence of the strongest respiratory stimulus that can be applied, carbon dioxid.

TABLE 2

Vital capacity and tidal air

NUMBER AND NAME	VITAL CAPACITY	CALCULATED VITAL CAPACITY LUNDSGAARD	RESTING TIDAL AIR	TIDAL AIR AT END OF REBREATHING	DIAGNOSIS AND REMARKS
1. D. P. B...	4537	3332*	580	2407	Normal
2. J. P.....	3953	3704	372	1929	Normal
3. T. deC....	3839			1249	Cardiac. Compensated
4. P. K.....	3503		371	1192	Gastric neurosis
5. A. J.....	2729		389	980	Shell shock. Effort syndrome
6. J. B.....	2519		737	1236	Cardiac. Slight dyspnea and hyperpnea
7. J. C.....	2432	2980	421		Cardiac. Compensated
8. J. A.....	2430	2930	439	1116	Cardiac. Compensated
9. C. D.....	2145		315	581	Cardiac. Severe decompensation
10. J. M. L...	1789		390	1309	Cardiac. No dyspnea nor hyperpnea
11. A. R.....	1789	3640	604		Nephritic. Mild acidosis
12. R. W.....	1714	3930	244		Cardiac. Some dyspnea
13. J. J. F....	1704		304		Cardio-nephritic. Mild acidosis
14. W. W.....	1452	4698	469		Cardiac. Some dyspnea
15. D. O. C...	1303	3540	423	638	Cardiac. Marked dyspnea
16. S. I.....	1248		375		Cardiac. Severe dyspnea
17. J. M.....	1197		475		Cardiac. Extreme cyanosis. Some dyspnea
18. Jos. C....	1182		385	492	Cardiac. Marked dyspnea

* See note, table 1.

Peabody (5) found the average resting tidal air slightly reduced in cardiac dyspnea. This our figures do not show. If such a reduction

exists it is small in proportion to the enormous reduction found in the vital capacity.

The maximum tidal air, on the other hand, varies almost directly with the vital capacity and the ratio between the two shows the same range of variation in cardiac patients with dyspnea as in normals (0.35 to 0.55). Number 10 is the only exception to this rule. In his case the "maximum tidal air" was very large in proportion to the vital capacity. It was noted in the course of the experiment on this patient that he could not be induced to exert himself to the full extent of his strength when he blew into the spirometer. The low vital capacity, in this instance, may be only an expression of lack of effort on the part of the patient. This was completely overcome under the stimulus of carbon dioxid and he showed a normal "maximum tidal air," although he did not continue rebreathing to the point of exhaustion.

In the case of the decompensated cardiac patients, however, there was no lack of effort apparent during the determination of the vital capacity. Moreover, two of them continued rebreathing to the point of extreme exhaustion. The reduction of the "maximum tidal air" and the vital capacity may be a functional matter, due to reflex inhibition. If so, this inhibition is so profound that it can not be overcome by the strongest stimulus which can be applied. The increase in the tidal air which normally occurs in response to the stimulus of carbon dioxid is limited by the lowered vital capacity.

DISCUSSION

Siebeck (1), in 1912, measured the lung volume in a series of cardiac patients by a rebreathing method. His studies showed that in cardiac dyspnea the residual air was relatively increased, although the absolute values he obtained seem to have been lower than normal. The reserve air and the complementary air were both decreased. These results are substantially the same as ours. However, Siebeck regarded them as questionable because he was unable to obtain the same constancy in his rebreathed mixtures in cardiac patients as in normals. In the latter the concentration of hydrogen in the rebreathing bag became constant after 5 respirations. In subjects with cardiac dyspnea the concentration continued to change even after 10 respirations. This Siebeck considered to be due to improper diffusion of air in the lungs. He concluded that the actual volume of residual air was greater than that indicated by the rebreathing methods.

As Sonne (6) has shown, the residual air can be measured with only an approximate degree of accuracy even in the normal person. Whether Siebeck is right in believing that the amount of air present is greater than that found, we are unwilling to argue. In two or three cases the number of respirations, the time and the volume of air rebreathed were varied without significant changes in the values obtained. This does not agree with Siebeck's findings. But any air that may be present and undetected must be peculiarly useless for respiratory purposes. A functional conception of the lungs is of more value than a purely anatomical one. In a normal person residual air determinations may be considered as measurements of the volume of air space in the fully deflated lungs, which is available for the rapid diffusion of gases. In this sense, certainly, the residual air is not increased in cardiac dyspnea. Since the vital capacity is decreased the effective volume of the lungs must be diminished.

Whether this diminution is due to a true anatomical lesion or not, we are unprepared to say. In some instances hydrothorax plays a part, but it is by no means an essential part. This we may assume not only because of the absence of physical signs of fluid, but also because of the rapidity with which the vital capacity increases as compensation is established (7).

Just what effect such a diminution of the lung volume may have on the gas exchange must be largely a matter of speculation until the cause of the diminution is determined. If it is not due to a true anatomical lesion it is quite possible that some or all of the blood in the pulmonary vessels is not in gaseous equilibrium with the alveolar air. This might, in part at least, explain the discrepancy between the alveolar CO_2 and the CO_2-combining capacity of the plasma.

This discrepancy Pearce (8) has attributed entirely to the effect of stasis in the general circulation. He has drawn a fine distinction between the causes of the low alveolar CO_2-tension in congenital heart disease, pneumonia and acquired heart disease. In congenital heart disease part of the venous blood does not pass through the lungs, and in consequence is given no opportunity to rid itself of the CO_2 which it has received from the tissues. In consequence the arterial blood is a mixture of aërated and unaërated blood. If there were no compensatory reaction a true carbon dioxid acidosis would occur. The respiratory mechanism, however, responds to the stimulus of the carbon dioxid. The alveolar CO_2-tension and the CO_2-tension of the blood which does pass through the pulmonary circulation is reduced suffi-

ciently to restore the CO_2-tension and hydrogen-ion concentration of the arterial blood to normal.

In patients with pneumonia in whom Pearce found the same discrepancy between the alveolar CO_2-tension and the plasma bicarbonates, he advances a similar explanation. In this case, although all the blood passes through the pulmonary circulation, he supposes that part of the blood passes through non-aërated portions of the lungs. On what seems to us insufficient evidence, he denies the possibility of such a condition in acquired cardiac disease. But certainly the reduction of the effective lung volume renders it not only possible, but not improbable. Even if Siebeck is right and this diminution is not due to a decrease in the actual air-containing space in the lungs, a certain part of this air must be unavailable for the rapid diffusion of gases and that portion of blood in the pulmonary circulation which comes in contact with this air must be less effectively ventilated than normal.

That the blood flow is retarded in decompensated cardiac disease is probable in the light of Harrop's (9) observation of an increase in the difference of the oxygen content of arterial and venous blood.

That this is the sole factor in the production of the low alveolar CO_2 remains to be proved. It is doubtful whether the method of Christiansen, Douglas and Haldane (10), which was employed by Pearce for the determination of the rate of blood flow, can be interpreted quantitatively in cardiac dyspnea. In this method it is assumed that the CO_2-tension of the alveolar air is the same as that of the arterial blood. That such a relation obtains in cardiac dyspnea demands definite proof. The use of respiratory methods that are designed to determine the venous CO_2-tension is also open to question when applied to conditions in which the venous oxygen unsaturation is excessive. Christiansen, Douglas and Haldane showed that the effect of oxygen on the carbon dioxid dissociation curve necessitated the introduction of a correction for the oxygen unsaturation even in normal persons. The extent of this correction in cardiacs can only be guessed.

Although the effect of the small effective lung volume on the exchange of gases between the blood and the alveolar air remains largely a matter of speculation, its effect on the mechanics of respiration is fairly clear. Here we have to deal only with the vital capacity, the portion of the lung volume available for ventilation of the lungs.

Apparently the reduction of vital capacity which occurs during cardiac dyspnea has little effect in limiting the respiratory exchange

during rest. The volume of the resting tidal air is not diminished. On the other hand, the amount by which the tidal air can increase under the stimulus of carbon dioxid seems to be distinctly limited by the reduction of the vital capacity. The reserve of the mechanical apparatus of respiration is therefore greatly diminished.

CONCLUSIONS

1. In cardiac patients with dyspnea no evidence of an increased residual air was obtained by the Lundsgaard method.

2. As the vital capacity is diminished, this means that the effective lung volume, the volume of air in the lungs available for the exchange of gases, is diminished.

3. The maximum volume of tidal air attained under the stimulus of continuous rebreathing is lower than normal in cardiac dyspnea. The reduction in the maximal tidal air bears a close relation to the reduction in vital capacity.

BIBLIOGRAPHY

(1) Siebeck: Deutsch. Arch. f. klin. Med., 1912, cvii, 253.
(2) McClure and Peabody: Journ. Amer. Med Assoc., 1917, lxix, 1954.
(3) Lundsgaard and Van Slyke: Journ. Exper. Med., 1918, xxvii, 65.
(4) Peters and Barr: This Journal (no. I of this series).
(5) Peabody, Wentworth and Barker: Arch. Int. Med., 1917, xx, 468.
(6) Sonne: Journ. Physiol., 1918, lii, 75.
(7) West: Paper read before the Section on Medicine of the New York Academy of Medicine, April, 1920.
(8) Pearce: Journ. Lab. Clin. Med., 1917, ii, no. 12.
(9) Harrop: Journ. Exper., Med., 1919, xxx, 241.
(10) Christiansen, Douglas and Haldane: Journ. Physiol., 1914, xlviii, 244.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

III. The Effective Ventilation in Cardiac Dyspnea

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In the previous papers of this series (1), (2) it has been shown that the effective lung volume is decreased during the dyspnea of cardiac decompensation. The alveolar CO_2 tension, as determined by the Haldane method, is usually low and always lower than the concentration of the bicarbonate in the venous plasma would indicate. We have shown that the air obtained by Haldane's method is probably true alveolar or exchange air. In this paper we shall present evidence to substantiate this contention and shall discuss the influence of a low alveolar CO_2 tension and of a diminished lung volume upon the effective ventilation in relation to the dyspnea of heart disease.

Peabody, Wentworth and Barker (3) find that, although the level of metabolism is normal or only moderately increased during cardiac decompensation, the minute volume of respiration is much greater than in normal individuals. The increase is accomplished by a more rapid respiratory rate with a moderate diminution in the volume of each expiration. The percentage of CO_2 in the expired air is diminished.

Peabody recognizes that the greater observed minute volume may represent no increase in the amount of effective air breathed. The tidal air consists of two parts. The dead space, which fills the upper respiratory tract is practically atmospheric air and is of no value in the ventilation of the functioning portions of the lungs. It is only the remainder of an expiration, the exchange air, which is effective for purposes of respiration. In any given expiration, the relative proportion of dead space to exchange air will determine the efficiency of ventilation. If, as Peabody assumes, the volume of the dead space is not changed during decompensation while the volume of tidal air

is diminished, the amount of effective air in each expiration will be diminished.

It is possible to arrive at a rough estimate of the effective minute volume by subtracting an average dead space value from the volume of the tidal air and multiplying the remainder by the respiratory rate. Different observers, Haldane and Priestley (4), Krogh and Lindhard (5) and Pearce (6), have found the volume of the dead space in normal resting subjects to vary between 100 and 200 cc. with an average of about 130 cc. Since there is no evidence that the dead space is changed in cardiac dyspnea and experiments reported in a previous paper (1) indicate that it cannot be greatly above the normal values, 130 cc. has been used as the average volume of the dead space for purposes of calculation.

To determine the effective ventilation, we made a considerable number of observations on the minute volume of normal individuals and of compensated and decompensated cardiacs. The method did not differ from that of Peabody except that a nose clip and rubber mouthpiece were substituted for the Siebe Gorman mask. The instrumental dead space was 30 cc. The expiratory air was collected in an accurately balanced Tissot spirometer for periods varying from five to ten minutes, the volume of expiration and the number of respirations being recorded for each minute. Volumes were reduced to standard conditions of 760 mm. Hg. and 0°C. To these observations we applied the following formula:

(Tidal Air − 160[1]) Respiratory Rate = Effective Minute Volume

The results are tabulated in table 1.

For the purpose of comparing our results with those of Peabody we have calculated the effective minute volume from his figures. The dead space of the Siebe Gorman mask which he used has been estimated at about 50 cc. Averages of the results are given in table 2.

The results of the two experiments are in practical agreement. In the decompensated cases, the minute volume of respiration is greater and the respiratory rate is increased. The volume of the tidal air is sometimes slightly diminished but this is by no means invariable as is shown by the large tidal air of J. B. and J. D. B. (table 1). The effective minute volume is much greater during decompensation.

It might be argued that the increase in effective ventilation is due to the higher level of metabolism and the consequent increase in CO_2

[1] To the average dead space of the individual has been added the instrumental dead space of 30 cc.

production which is observed in many dyspneic cardiac patients. That this is not true can be demonstrated by calculations from Peabody's figures (table 3).

Figures for surface area show that the average size of the patients in the two groups is practically identical. Differences either in the production of CO_2 or in the effective ventilation cannot be due to discrepancies in size. The CO_2 production per minute is only 5.1 per cent greater in the decompensated cases. The volume of effective air breathed per minute is 30.3 per cent higher than in the cases without

TABLE 1

SUBJECT	MINUTE VOLUME	TIDAL AIR	RESPIRATIONS PER MINUTE	EFFECTIVE MINUTE VOLUME	DIAGNOSIS AND REMARKS
	cc.	*cc.*			
D. P. B.	6,900	532	13.0	4,822	Normal adult
	6,789	580	11.7	4,913	
	6,040	592	10.2	4,406	
	6,751	668	10.1	5,131	
J. P.	5,524	372	14.9	3,148	Normal adult
	4,898	389	12.6	2,885	
	7,127	520	13.7	4,943	
G. C. D.	6,386	484	13.2	4,277	Normal adult
	6,243	488	12.8	4,198	
P. K.	4,659	293	15.9	2,115	Gastric neurosis. No sign of cardiac or pulmonary disease
	7,764	371	20.9	4,420	
Cap.	7,866	333	23.6	4,083	Normal adult. Respirations rapid and variable. Obviously over-ventilating
J. A.	6,474	439	14.8	4,106	Chronic cardiac valvular disease. No dyspnea while at rest in bed
	7,611	408	18.6	4,626	
J. M. L.	4,553	390	11.6	2,675	Chronic cardiac valvular disease. No dyspnea while at rest in bed
	6,133	438	14.0	3,893	
R. W.	5,826	244	23.9	2,003	Chronic cardiac valvular disease. Breathing quietly while at rest in bed. Rapid and superficial during experiment
J. W.	7,680	410	18.7	4,675	Chronic nephritis. Hypertension. No dyspnea while at rest in bed
Average	6,401	442	15.2	3,973	

TABLE 1—*Concluded*

SUBJECT	MINUTE VOLUME	TIDAL AIR	RESPIRATIONS PER MINUTE	EFFECTIVE MINUTE VOLUME	DIAGNOSIS AND REMARKS
	cc.	*cc.*			
J. B.	13,170	737	17.9	10,310	Chronic cardiac valvular disease. Dyspnea and cyanosis while at rest
	10,210	612	16.7	7,540	
Jos. C.	13,590	385	35.3	7,936	Chronic nephritis with hypertension. Severe cardiac decompensation with marked dyspnea
	14,140	350	40.3	7,638	
C. D.	9,982	315	31.8	4,916	Chronic cardiac valvular disease. Severe dyspnea and orthopnea
S. I.	6,930	375	18.5	3,970	Chronic cardiac valvular disease. Massive hydrothorax. Dyspnea and orthopnea
D. O. C.	8,069	423	19.1	5,020	Chronic cardiac valvular disease. Marked cyanosis and moderate dyspnea while at rest. Right hydrothorax
W. W.	9,528	469	20.3	6,279	Chronic cardiac valvular disease. Moderate dyspnea while at rest
J. R.	11,393	311	36.7	5,542	Chronic cardiac valvular disease. Marked dyspnea and orthopnea while at rest
	10,110	357	28.3	5,575	
P. O. S.	9,087	279	32.6	3,879	Chronic cardiac valvular disease. Right hydrothorax. Marked dyspnea and orthopnea while at rest
J. D. B.	14,310	821	17.4	11,501	Chronic cardiac valvular disease. Marked dyspnea and orthopnea while at rest
	12,800	538	23.8	8,996	
J. M.	8,652	475	18.2	5,733	Chronic cardiac valvular disease. Extreme cyanosis and some dyspnea while at rest
	9,843	496	19.8	6,653	
Average	10,788	463	25.1	6,766	

dyspnea. Only a small part of the increase in effective ventilation can be accounted for by a greater CO_2 production.

Furthermore, since the dyspneic cardiac breathes a much greater amount of CO_2, each volume of his effective or alveolar air must contain a smaller percentage of CO_2.

TABLE 2

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Minute volume (cc.*)	5,901	8,521
Tidal air (cc.)	466	398
Respiratory rate	13.2	21.8
Effective minute volume (cc.)	3,530	4,600

* Minute volumes have been recalculated from the CO_2 produced per minute and the percentage of CO_2 in the expired air.

TABLE 3

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Surface area (square meters)	1.72	1.77
CO_2 production per minute (cc.)	196	206
Effective minute volume (cc.)	3,530	4,600

It is possible to show more directly the probability of a reduced alveolar CO_2 tension. In the paper describing their method of obtaining alveolar air, Haldane and Priestley (4) indicated a means of determining the volume of the dead space. The data necessary for the calculation were the volume of an expiration, the percentage of CO_2 in the expired air and the percentage of CO_2 in the alveolar air. These were combined in the following formula:

Formula I

$$\text{Tidal air} - \frac{\text{Tidal air} \times \text{per cent } CO_2 \text{ in expired air}}{\text{Per cent } CO_2 \text{ in alveolar air}} = \text{Dead space}$$

By a simple inversion of their formula, the percentage of CO_2 in the alveolar air can be deduced.

Formula II

$$\frac{\text{Tidal air} \times \text{per cent } CO_2 \text{ in expired air}}{\text{Tidal air} - \text{Dead space}} = \text{Per cent } CO_2 \text{ in alveolar air}$$

Both of these formulae were applied to observations on a number of normal individuals and on cardiacs in varying degrees of decompensation. Minute volume determinations were made as in the previous experiments. At the close of an observation, the air was thoroughly mixed in the spirometer and a sample was taken for analysis. Haldane

TABLE 4

SUBJECT	MINUTE VOLUME	RESPIRATIONS PER MINUTE	TIDAL AIR	CO_2 IN EXPIRED AIR	ALVEOLAR CO_2 CALCULATED FROM DEAD SPACE FORMULA	ALVEOLAR CO_2 OBSERVED HALDANE METHOD	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DEAD SPACE CALCULATED FROM		DIAGNOSIS AND REMARKS
								Observed alveolar CO_2	Alveolar CO_2 calculated from plasma	
	cc.		*cc.*	*per cent*	*per cent*	*per cent*	*per cent*	*cc.*	*cc.*	
D. P. B.	6,040	10.2	592	3.92	5.39	5.39		130		Normal adult
	6,751	10.1	668	4.16	5.47	5.40		123		
J. P.	4,898	12.6	389	3.84	6.52	5.89		105		Normal adult
	7,127	13.7	520	4.29	6.14	5.75		132		
Cap.	7,866	23.6	333	3.27	6.29	6.31		130		Normal adult
G. C. D.	6,386	13.2	484	3.42	5.11	6.39		195		Normal adult
	6,248	12.8	488	4.04	6.01	6.63		161		
J. W.	7,680	18.7	410	3.03	4.98	4.85	5.60	124	158	Chronic cardiac valvular disease. No dyspnea while at rest
Average	6,625	14.4	486	3.75	5.74	5.83		138		
J. R.	11,396	36.7	311	2.16	4.44	4.60	6.73	139	181	Chronic cardiac valvular disease. Dyspnea and orthopnea while at rest
	10,110	28.3	357	2.33	4.26	3.95		115		
J. D. B.	14,310	17.4	821	2.14	2.66	3.11	5.53	226	473	Chronic cardiac valvular disease. Moderate dyspnea and cyanosis
	12,800	23.8	538	2.69	3.82	4.53		189		
J. M.	8,652	18.2	475	2.40	3.62	3.39	5.76	109	247	Chronic cardiac valvular disease. Extreme cyanosis, moderate dyspnea
	9,843	19.8	496	2.72	4.02	4.96	7.41	195	284	
P. O. S.	9,087	32.6	279	2.30	5.39	5.69	7.40	136	162	Chronic cardiac valvular disease. Severe decompensation with dyspnea and orthopnea
Average	10,885	25.2	469	2.39	4.03	4.32		159		

samples of alveolar air were taken before and after the minute volume determinations. A specimen of blood was drawn from an arm vein for determination of the bicarbonates in the plasma. The results obtained from the plasma were converted into terms of percentage of alveolar CO_2 according to the method of Van Slyke (7).

In formula II, average dead space values were employed for the calculation of the probable percentage of CO_2 in alveolar air. The results are recorded in table 4 (column 6). They agree closely with the results of direct observation by the Haldane method (column 7) and consequently in the decompensated cardiac lie far below the value indicated by the plasma (column 8).

In formula I, the observed alveolar CO_2 per cent and the percentage indicated by the plasma have been applied to calculate the probable dead space. Substitution of the observed values give volumes of dead space which are within the range of normal (column 9) while substitution of percentages indicated by the plasma give decidedly improbable results (column 10).

Formula II has also been applied to Peabody's figures. Averages are given in table 5.

TABLE 5

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Tidal air (cc.)	466	398
CO_2 in expired air (per cent)	3.35	2.44
Calculated alveolar CO_2 per cent (using dead space of 180 cc.)*	5.72	4.70

* Average dead space of 130 cc. to which is added the extra dead space of 50 cc., the capacity of the Siebe Gorman mask.

Both in Peabody's figures and in ours, the percentage of CO_2 in the alveolar air is lower during decompensation.

DISCUSSION

In this series of papers the question of the concentration of CO_2 in alveolar air during cardiac decompensation has been approached from several angles. Of the direct methods, that of Haldane which has been found applicable to dyspneic patients gives values for alveolar CO_2 percentage much lower than it does in normal individuals. Duplicate samples, however, show quite as close agreement in dyspneic

cardiacs as in trained normal subjects. Experiments have shown that the low content is not due to subjective errors nor to an increased dead space. After breathing increasing percentages of CO_2, the alveolar CO_2 percentage of dyspneic cardiacs is still relatively lower than it is in normal individuals under the same circumstances. The percentage, moreover, is not increased by increasing the depth of expiration. An expiration of maximum depth contains no greater concentration of CO_2 than does one of a volume just sufficient to clear the dead space. Whether the specimen of air obtained by the Haldane method is from the alveoli or from other portions of the lungs is not of great importance in the present discussion. Whatever the anatomical source of the sample may be, it is the only air which by the greatest effort the decompensated cardiac can expire. It is the only air which can be functionally effective in the elimination of CO_2 from the body. If this is true the CO_2 contained in this air should completely account for the total CO_2 elimination. In this paper it has been shown by the use of Haldane's dead space formula that the percentage of CO_2 found in the Haldane specimen is the percentage theoretically required to account for the CO_2 eliminated.

The accumulated evidence, both direct and circumstantial, indicates that the percentage of CO_2 is low in the effective air of dyspneic cardiac subjects. The cause of this important phenomenon is not clearly understood. Its chief importance in the present discussion lies in its effect upon the ventilation in cardiac disease.

A low percentage of CO_2 in the effective air necessitates a larger effective ventilation to accomplish CO_2 elimination. Even when the metabolism is normal, the decompensated cardiac exhibits hyperpnea. As long as he lies quietly in bed, this usually involves an increase in the rate of respiration with little or no change in the volume of each respiration. Under these circumstances the low effective lung volume, which is the constant accompaniment of decompensation, is not a factor of great importance in the causation of dyspnea. It probably exerts a greater influence during conditions involving a greater production of CO_2.

Concerning the mechanism of ventilation during exercise, we have accumulated no direct evidence. A good indication of the response is furnished, however, by experiments upon the rebreathing of CO_2. Under these circumstances the cardiac is subjected to a most powerful stimulus to respiration. The mechanism should, by analogy, be similar to that occurring during exercise or any other condition involving a

rapid production of CO_2 within the body. It has been shown that the cardiac maintains a relatively low alveolar CO_2 percentage during rebreathing. To accomplish this he must breathe a larger volume of effective air. Under the stimulus of CO_2, the volume of the tidal air increases both in cardiacs and in normal individuals. The increase, however, is in proportion to the vital capacity. In both groups the tidal air reaches a maximum at one-third to one-half of the volume of the vital capacity. Thus, a normal individual with an original vital capacity of 4000 cc. may show under the stimulus of CO_2 a tidal air of 1500 to 2000 cc. In a decompensated cardiac whose vital capacity may be only 1500 cc. the tidal air will not rise above 500 to 750 cc. with maximum CO_2 stimulation. The volume of respiration is strictly limited. Any attempt to increase it is accompanied by marked subjective dyspnea.

Two factors in cardiac disease help to explain the dyspnea which is its most constant subjective symptom. The low percentage of CO_2 in the effective air makes an increase in ventilation essential. The diminished effective lung volume makes any large increase difficult or impossible. The first is active under all conditions while the cardiac is decompensated. The second exerts its chief influence when the production of CO_2 in the body is increased.

CONCLUSIONS

1. Air obtained from decompensated cardiacs by the Haldane alveolar method is true exchange air. It corresponds to the alveolar air obtained by the same method in normal resting subjects. It is the only air effective for the elimination of CO_2.

2. During cardiac dyspnea, the bicarbonate content of the plasma gives no indication of the percentage of CO_2 in the exchange air.

3. The minute volume of effective or exchange air is increased during cardiac decompensation.

4. This is not explained by the higher level of metabolism.

5. The greater effective ventilation is necessitated by the low concentration of CO_2 in the exchange air.

6. Great increases in ventilation are impossible because of the diminished effective lung volume of decompensated cardiacs.

BIBLIOGRAPHY

(1) Peters and Barr: This Journal, this series, no. I.
(2) Peters and Barr: This Journal, this series, no. II.
(3) Peabody, Wentworth and Barker: Arch. Int. Med., 1917, xx, 468.
(4) Haldane and Priestley: Journ. Physiol., 1905, xxxii, 240.
(5) Krogh and Lindhard: Journ. Physiol., 1917, xliii, 73.
(6) Pearce: This Journal, 1917, xliv, 391.
(7) Van Slyke, Stillman and Cullen: Journ. Biol. Chem., 1917, xxx, 401.

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I. THE CARBON DIOXIDE ABSORPTION CURVE AND CARBON DIOXIDE TENSION OF THE BLOOD OF NORMAL RESTING INDIVIDUALS.

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INTRODUCTION.

In 1919 Haggard and Henderson (1) outlined a method for the direct determination of the carbon dioxide tension of arterial and venous blood. They also demonstrated the applicability of the method to the study of abnormal physiological conditions involving disturbances of the respiratory system and the acid-base equilibrium in the blood. Stadie's (2) demonstration of the practicability of arterial puncture as a safe procedure suggested the application of Haggard and Henderson's method to the study of problems of human physiology and pathology. The method consisted of the simultaneous determination of the carbon dioxide absorption curve of the blood and the carbon dioxide content of the arterial and venous blood. By interpolating the arterial and venous values on the absorption curve the carbon dioxide tension and hydrogen ion concentration of the blood as they existed in the body were estimated. This method, with such modifications as were necessary to render it applicable to work with human subjects, has been employed by us in the study of a series of normal and pathological subjects.

In brief the procedure followed has been to obtain specimens of arterial and venous blood simultaneously, protecting them from contact with the air and consequent loss of CO_2 by means of albolene. Just before and just after the arterial puncture specimens of alveolar air were obtained by the Haldane and Priestley method (3). The carbon dioxide and oxygen content of both

arterial and venous specimens and the oxygen capacity of the blood were determined at once. Specimens of the blood (usually venous) were then exposed to various mixtures of CO_2 and air at 37.5°C. The carbon dioxide content of each specimen was measured and the absorption curve obtained from the results. The values for the CO_2 content of the arterial and venous blood and the CO_2 tension of the alveolar air were then placed on the curve by interpolation. In many cases we determined also the CO_2 capacity of the venous plasma.

This work was practically completed when Means (4) presented before The Association of American Physicians the results obtained by the application to fifteen normal and pathological subjects of a method for determining arterial carbon dioxide tension similar in all essential respects to our own. Means confined his efforts entirely to a determination of the absorption curve and the arterial CO_2 tension. To this we have added several other factors, especially the alveolar CO_2 tension. This has led us to draw different conclusions with regard to certain points. Dr. Means has kindly permitted us to see his paper in manuscript form so that we are able to call attention to these differences at this time.

Before this method could be applied to the study of pathological subjects it seemed necessary to ascertain the limits of variation of the various factors involved, in normal persons. As the subjects of this investigation three adult males were employed: J. P. (Case 1) and D. P. B. (Case 3), two of the authors of the paper; and W. S. M. (Case 2), Dr. William S. McCann, whose assistance in this respect and in other parts of the work we gratefully acknowledge. All three subjects had successfully passed examinations for the Medical Corps of the United States Army and on subsequent examinations had shown no signs of any existing pathological condition or abnormality that could in any way render their use as normal controls open to question. It will appear in the course of this investigation that some of our results fall definitely outside what has hitherto been considered as the range of normal variation. These deviations may be due to faults in the theory or methods employed by us or by previous observers. It may be that the amount of normal control material hitherto available has been too small to cover the entire range of

normal variation. It is possible that subsequent developments may prove that the deviations are indications in our subjects of pathological conditions at present undemonstrable by other methods.

The use of only three normal subjects offers an entirely inadequate amount of control material. The scope and nature of the investigation rendered it difficult to make a more extensive study. Of course it would have been possible to make use of selected patients in the hospital and thus enlarge the number of individuals in this group. The use of patients with pathological conditions as normal controls is, however, open to criticism in any investigation in which the influence of all factors attending these pathological conditions is not definitely established. The limits of variation of the carbon dioxide absorption curve as established by Straub and Meier (5) from a study of 56 hospital patients whose clinical condition, they say, gave no reason to suspect any pathological change of the blood, are very different from the limits of variation found by all other observers in known normal individuals.

If it were necessary to rely entirely on the results of our own observations for the delimitation of normal variations, certainly our material is inadequate. There is, however, a considerable mass of experimental data in the literature which we have employed freely for comparison and corroboration.

Details of Method as Applied to Both Normal and Pathological Subjects.

The experiments on patients were usually performed in the afternoon, about 2 hours after the midday meal. In some cases they were begun in the morning, 4 hours or more after breakfast. No attempt to establish standard dietary conditions was made. Most of the patients were unable to get out of bed. In the few cases in which the condition of the subject permitted him to be up and about, a preliminary rest period of 30 minutes was given. During this time the patient remained in the reclining position. The experiments on normal persons were usually performed very shortly after the midday meal and were preceded by a 30 minute rest period.

Specimens of alveolar air were obtained both before and after the arterial puncture. The arterial puncture was done under novocaine anesthesia. The blood was withdrawn under albolene into a Luer syringe and then placed under albolene in a test-tube from which specimens were removed for analysis within a few minutes.

The venous blood was collected as soon as possible after the arterial puncture. To prevent venous stasis no tourniquet was applied and the subject was directed to keep his arm relaxed. The blood was collected under albolene, without any contact with the air.

Coagulation of the blood was prevented by the addition of a minimal amount of dry, neutral potassium oxalate.

As soon as possible after the blood had been obtained from the subject under investigation, 3 cc. portions were placed in cylindrical separatory funnels of about 300 cc. capacity. These were filled with a mixture of CO_2 and air. The mixture was made up in a cylinder of about 1,200 cc. capacity and passed through the separatory funnel in an interrupted stream in order to wash the funnel out completely. Simultaneous analysis of the air in the cylinder and that in the separatory funnel showed differences of 0.2 per cent or less, indicating that the method was sufficiently accurate for our purposes. The mixture in the cylinder was analyzed for carbon dioxide each time. The distal opening of the separatory funnel was tightly stoppered while the gas was still flowing through it, and the pressure equalized by water level in the cylinder. The proximal stop-cock was now shut off and the separatory funnel rotated in a water bath at 37.5°C. for 20 minutes. As it was rotated with its long axis in the horizontal position a maximum blood surface was exposed to the gas mixture. At the end of the 20 minute period rotation was discontinued and the separatory funnel was placed in the vertical position long enough to allow the blood to collect in the narrowest portion. The neck was now withdrawn from the bath and carefully dried. The stopper was then removed and duplicate specimens were withdrawn by two observers as rapidly as possible in Ostwald pipettes calibrated to deliver 1 cc. between two points.

The carbon dioxide content of both specimens was determined simultaneously in two Van Slyke pipettes. The technique was the same as that described by Van Slyke (6) except for the fact that 20 per cent tartaric acid was substituted for N sulfuric. The coagulum produced by tartaric acid in whole blood is not so firm as that produced by sulfuric and consequently does not clog the pipette or render it difficult to clean. The blood was introduced into the cup of the pipette beneath a drop of dilute, carbon dioxide-free ammonia water to prevent the escape of CO_2. A blank determination of CO_2 in the reagents was made with each experiment and subtracted from the observed reading. This correction was rendered as small as possible by the use of carbon dioxide-free water and ammonia water. It was usually about 0.01 cc. On one or two occasions it rose to 0.02 or 0.025 cc.

Calculation and Extent of Error.

Owing to the fact that the gas mixture in the separatory funnel was equilibrated with atmospheric pressure at room temperature only, and not at 37.5°C., a correction had to be made for the altered CO_2 tension caused by the change in temperature, and for the vapor pressure. This should intro-

duce no error, as the concentration of carbon dioxide in solution is dependent directly on the carbon dioxide tension of the atmosphere with which it is in contact. The error that may occur from incomplete washing out of the separatory funnel is, as we have stated, less than 0.2 per cent, or 1.5 mm., and must lie always in the same direction. A further slight error is introduced by the loss or gain of CO_2 by the blood in coming to equilibrium with the air in the separatory funnel. This must be very small and can be more or less accurately estimated. The maximum amount of CO_2 change from this source was only 0.2 to 0.3 cc. per cc. of blood. With 3 cc. of blood in a 300 cc. separatory funnel this again might produce a change of 1.5 to 2.0 mm. in the CO_2 tension of the gas mixture. In point of fact this change must have been very much smaller in most instances. The error thus produced will vary in direction and extent according to the original carbon dioxide content of the blood. Roughly we may say that at carbon dioxide tensions below that of the blood employed the apparent CO_2 tension cannot be more than 1.5 mm. above or below the actual and most usually be much less, because the two main sources of error tend to compensate one another. At carbon dioxide tensions above that of the blood the apparent CO_2 tension may be as much as 3 mm. too high.

Duplicate determinations with the Van Slyke pipette should differ by not more than 1 volume per cent. Occasionally such agreement was not obtained. Sometimes this was directly referable to errors in technique; in some instances no such errors were discovered. The faulty agreement in these cases may have been occasioned by some loss of CO_2 due to a delay in the transfer of the blood from the separatory funnel to the pipette. On the whole we believe that this was a minimal source of error. The blood was withdrawn from the funnels with the least possible loss of time. Although we have made no direct experiments to determine the rate of loss of CO_2 under these conditions the fact that duplicate samples check so accurately in most instances indicates that such loss must be very slight.

A certain error is introduced by the volumetric measurement of small amounts of blood. The pipettes were carefully calibrated to deliver 1 cc. of distilled water between two marks with an accuracy of ± 0.002 cc. The error entailed in measuring a viscous solution like blood must vary with the physical characteristics of the individual specimen under investigation and cannot be estimated, but can never be entirely negligible. It must lie always in the same direction and tend to make the apparent volume of carbon dioxide too low.

Van Slyke (6) showed that the addition of potassium oxalate to plasma did not affect its carbon dioxide-combining capacity. De Corral (7) found that anticoagulant concentrations of potassium oxalate produced no recognizable effect on the hydrogen ion concentration of whole blood. In this case it should also be without effect on the carbon dioxide-combining capacity of whole blood. Joffe and Poulton (8), in point of fact, could demonstrate no change in the level of the absorption curve of fully-oxygenated blood as a result of the addition of oxalate. This seems hardly possible, however, in view of the extreme lability and sensitiveness of the

ionic balance between cells and plasma. We have attempted to determine the presence and extent of the changes produced by the addition of potassium oxalate to whole blood.

Blood was drawn into a tube containing 1 mg. of hirudin for each 2.5 cc. of blood. 2 cc. portions of this blood were placed in two separatory funnels. To the blood in one of these were added 40 mg. of crystalline, neutral potassium oxalate. Both funnels were then filled with the same air-CO_2 mixture from a large spirometer and rotated at room temperature for 15 minutes. At the end of this time both specimens of blood were analyzed for CO_2 by the Van Slyke method. Other samples of blood were defibrinated and the effect of adding oxalate to defibrinated blood was also determined. The results appear in Table I.

TABLE I.

Effect of Potassium Oxalate in a Concentration of 2 Per Cent on the Carbon Dioxide-Combining Capacity of Blood.

	CO_2 content of blood after exposure to the same air-CO_2 mixture.		
	Without oxalate.	With oxalate.	Difference.
	cc.	*cc.*	*cc.*
Hirudinized blood.	0.685	0.686	+0.001
	0.696	0.734	+0.038
	0.696	0.728	+0.032
	0.559	0.620	+0.061
	0.597	0.695	+0.098
	0.569	0.600	+0.031
	0.554	0.618	+0.064
Defibrinated blood.	0.648	0.677	+0.029
	0.635	0.688	+0.053
Average difference			0.045

The addition of potassium oxalate in 2 per cent concentration produces an average increase of about 4 volumes per cent in the CO_2-combining capacity of the whole blood. This change occurs whether the oxalate is added to hirudinized or defibrinated blood. The increase was not constant in magnitude in all the observations. However, in this concentration oxalate produces visible physical changes in blood. The blood appears a lighter and brighter red. Whether this is due to hemolysis or not was not determined. The variations in our results may be somewhat dependent on the speed with which the oxalate was dissolved.

The concentration of oxalate employed in this experiment was far in excess of that used for the purposes of preventing coagulation. Such a concentration was chosen for the preliminary observations in order to

insure the detection of any change that might occur. When it was found that this change was constant in direction, the experiment was repeated with only 10 mg. of oxalate to each 2 cc. of blood (see Table II). In this concentration (0.5 per cent) which is well above that used to prevent coagulation, no visible physical changes in the blood were detected. The addition of oxalate increases the carbon dioxide-combining power of blood only about 1 volume per cent.

Christiansen, Douglas, and Haldane (9) found that if blood was allowed to stand its CO_2 capacity gradually diminished as if it became more acid. This change occurred more rapidly at body temperature than at the temperature of the room. For this reason we have exposed a fresh sample of blood to each gas mixture. In this way no sample remained at 37.5°C. more than 20 minutes. However, the multiplicity of procedures, involved

TABLE II.

Effect of Potassium Oxalate in a Concentration of 0.5 Per Cent on the Carbon Dioxide-Combining Capacity of Blood.

	CO_2 content of blood after exposure to the same air-CO_2 mixture.		
	Without oxalate.	With oxalate.	Difference.
	cc.	cc.	cc.
Defibrinated blood.	0.599	0.622	+0.023
	0.612	0.632	+0.020
	0.624	0.628	+0.004
	0.748	0.755	+0.007
	0.745	0.742	−0.003
	0.787	0.810	+0.023
	0.797	0.793	−0.004
	0.785	0.808	+0.023
Average difference			+0.0116

in simultaneous studies of so many factors, prolonged the total time of the experiments more than we should have wished. When only the absorption curve was determined, the duration of the procedure was within the limits of safety; in the complete experiments this was not always the case.

The order of procedure in the laboratory was:

I. The simultaneous determination of

1. The carbon dioxide content of arterial blood (in duplicate).
2. The carbon dioxide content of venous blood (in duplicate).
3. The oxygen content of arterial blood.

II. The determination of the oxygen content of venous blood. (In the later experiments four Van Slyke pipettes were used and the arterial and venous bloods were analyzed for oxygen at the same time, one observer manipulating both oxygen pipettes and extracting one specimen while the other was being laked.)

III. Determination of the oxygen capacity of the blood.

IV. Determination of the absorption curve. (Unfortunately the size of the water bath permitted the introduction of only one separatory funnel at a time.)

TABLE III.

Effect of Time on the CO_2-Combining Capacity of Blood.

	Time after withdrawal of blood.	CO_2 content of blood.	Change of CO_2 content.
	min.	*cc.*	*cc.*
1. Hirudinized blood.	0	0.597	0.000
	120	0.569	−0.028
	165	0.554	−0.043
2. Defibrinated blood.	0	0.648	0.000
	60	0.635	−0.013
3. Defibrinated blood.	10	0.787	0.000
	65	0.797	+0.010
	170	0.785	−0.002
4. Oxalated blood.	30	0.720	0.000
	60	0.705	−0.015
	190	0.711	−0.009
	210	0.720	0.000
5. Oxalated blood.	5	0.790	0.000
	30	0.782	−0.008
	150	0.758	−0.032
	210	0.750	−0.040
6. Oxalated blood.	5	0.724	0.000
	60	0.723	−0.001
	125	0.703	−0.021
	180	0.676	−0.048
7. Defibrinated blood with 0.5 per cent oxalate.	10	0.810	0.000
	65	0.793	−0.013
	170	0.808	−0.002

In spite of the continuous work of three persons the total elapsed time of an experiment sometimes exceeded 3 hours. As skill and team work improved, this was steadily reduced until in the last observation we were able to complete the whole procedure within 2 hours from the time that the blood was withdrawn. It seemed advisable to find out the magnitude of the change which occurred in the blood on standing in the laboratory at

room temperature for this length of time. Blood was therefore withdrawn into oxalate and samples were removed at intervals, exposed to an air-CO_2 mixture, and the CO_2 content was measured. The results appear in Table III. Although not very consistent they indicate that the element of time may be a rather serious source of error. If blood is kept in an ordinary tube at room temperature, no change in the carbon dioxide-combining capacity can be demonstrated until the 2nd hour. At the end of 2½ hours a loss of about 2 per cent is found. After 3 hours this has increased to about 3 per cent. The fact that this loss occurred in some specimens, but not in others, suggests that it may be hastened by extraneous factors.

If all these errors should fall in the same direction one might conceivably obtain an absorption curve that was apparently 3.5 volumes per cent lower than the actual curve. The mean variation, however, is much smaller than this and cannot be considerably greater than the error of the actual measurement with the Van Slyke pipette. The general tendency is to make the curve low. The influence of these errors, in any case, cannot be very great as we are using the curves for the most part as a basis for comparative studies only.

Method of Representation.

In all charts the abscissa represents the carbon dioxide tension with which the blood is in equilibrium, expressed in mm. of mercury at 37.5°C., corrections having been made for the barometer and vapor tension. The ordinate represents the carbon dioxide content of whole blood, both physically dissolved and chemically combined. As the physically dissolved CO_2 is a direct linear function of the carbon dioxide tension, there is nothing to be gained by subtracting this from the total as is done by Haggard and Henderson (1).

For the calculation of the diagonals expressing pH, Henderson's formula has been used, modified to show the pH directly instead of his C_H7. The use of the negative logarithm, introduced by Sörensen, has become general and is convenient. The further multiplication of forms of expression can only tend to produce confusion and misunderstanding. The Henderson scale agrees fairly closely with that of Hasselbalch (10). That the calculation of the hydrogen ion concentration of the blood from the H_2CO_3: $BHCO_3$ ratio rests on a sound theoretical basis was first shown by L. J. Henderson (11). Hasselbalch (10) later demonstrated the accuracy of the method by practical experiments. Both Henderson and Hasselbalch dealt with completely oxygenated blood. Parsons (12) has recently questioned Hasselbalch's results on the ground that the application of the H_2CO_3:$BHCO_3$ ratio as a measure of hydrogen ion concentration is possible only in the case of homogeneous solutions such as plasma. Whole blood is a mixture consisting of two phases, cells and plasma. In a comparison of the hydrogen ion concentration measured electrometrically with that calculated by means of the H_2CO_3:$BHCO_3$ ratio in whole blood, Parsons found differences of as much as 0.09 in the pH. His values for pH are also

consistently higher than those of Hasselbalch. The difference of scale implied in the latter is of no importance if we use our figures only for comparative purposes. Until the point at issue is definitely settled it seems better to continue the use of the Hasselbalch pH scale with the realization that, if Parsons is correct, it should be rotated to the right 0.03 to 0.04 points. The discrepancy of 0.09 between calculated and observed values of pH found by Parsons indicates a considerable error in the method of calculation. This is, however, the maximum error. The average error, as we have calculated his results, is only about 0.03, if allowance is made for the difference in scale noted above. If we recognize the possibility of the presence of an error of this magnitude in our method of calculation we may use the values here obtained for purposes of comparison where the observed changes are large and consistent and occur in completely oxygenated blood. Work of Parsons (12) and L. J. Henderson (13) suggests that the application of the same scale to partially or completely reduced blood is not entirely proper because of the nature of hemoglobin. This will have little or no effect as regards the absorption curve figures, as these are determined on completely oxygenated blood. It may have considerable effect on the interpretation of the carbon dioxide content values of arterial and venous blood; but this will be discussed later. In any event each diagonal line must represent the locus of points on which the H_2CO_3:$BHCO_3$ ratio is identical.

The carbon dioxide capacity of the venous plasma is reduced to terms of alveolar carbon dioxide with which it should correspond if the normal relation found by Van Slyke obtained. The formula employed is

$$(\text{Mg. } CO_2 \text{ in chemical combination in 1 cc. plasma}) \times 35 = x$$

The Effect of Oxygen Unsaturation on the Carbon Dioxide Absorption Curve.

One difficulty at once presents itself. The absorption curve is obtained from completely oxygenated blood, while both the arterial and venous blood are partially reduced. Christiansen, Douglas, and Haldane (9), Hasselbalch (10), Parsons (12), and L. J. Henderson (13) have all shown that reduced blood has a greater power of combining with CO_2 than has oxygenated blood. All these observers employed defibrinated blood. Haggard and Henderson (14) reported recently that they had been unable to demonstrate this effect of oxygen on the absorption curve of oxalated blood. On the other hand Joffe and Poulton (8) found no difference in this respect between defibrinated and oxalated blood. The findings of the two observers are flatly contradictory. Collateral evidence, however, strongly favors the view of Joffe

and Poulton. The effect of oxygen unsaturation on the absorption of carbon dioxide in defibrinated blood is unquestionable. If oxygen unsaturation is without effect on the absorption curve of oxalated blood, the absorption curves of defibrinated and of oxalated venous blood should be quite different. Venous blood, as drawn, may be as much as 50 per cent unsaturated with oxygen. If this blood is defibrinated and then completely oxygenated, the usual procedure in the determination of the absorption curve, the change from partial reduction to complete oxygenation should make the absorption curve low in comparison with that of oxalated blood.

That this is not the case and that the carbon dioxide-combining capacity of oxalated blood is increased by oxygen unsaturation is shown by the following experiment.

50 cc. of blood were withdrawn from an arm vein of J. P. under albolene, without contact with the air. 25 cc. of this blood were defibrinated under albolene, while to the remainder was added a small amount of neutral potassium oxalate.

The oxygen content of both portions was then determined. The oxalated blood contained 7.1 volumes per cent of oxygen, representing an oxygen saturation of 33 per cent; the defibrinated portion contained 6.65 volumes per cent of oxygen, an oxygen saturation of 31 per cent.

Samples of each portion were then exposed for equal lengths of time to an air-CO_2 mixture of 38 mm. of CO_2 tension, at 37.5°C. Analysis at the end of this period gave 42.3 volumes per cent of CO_2 in the oxalated blood and 42.0 volumes per cent in the defibrinated. Both showed an oxygen saturation of 98.4 per cent.

Another sample of the oxalated blood was, at the same time, exposed to a mixture of CO_2 and nitrogen of 38 mm. of CO_2 tension. Analysis showed that this contained 47.5 volumes per cent of CO_2 and an oxygen saturation of only 21 per cent.

As a result of a reduction of 77.4 per cent in the oxygen saturation the carbon dioxide-combining power of the oxalated blood was increased 5.2 volumes per cent. This agreed with the value obtained by calculation from our empirical formula (see below), which was 5.66 volumes per cent.

That oxalated blood is suitable for the determination of the absorption curve is indicated by the experiments on the effect of oxalate detailed above (see "Methods"). Van Slyke and Cullen (15) have also shown that if arterial and venous bloods, oxalated, are exposed to the same mixture of CO_2 and air they are found to have the same carbon dioxide-combining power. If, then, oxygen does affect the carbon dioxide-combining power of blood in the

body, the addition of oxalate to the blood does not interfere with the reaction. As we shall point out later, unless such a reaction occurs in the body, certain respiratory phenomena become quite incomprehensible. At present the weight of evidence favors those who claim that oxygen influences the absorption of carbon dioxide in the blood. In this case arterial and venous carbon dioxide tensions must be corrected for oxygen unsaturation in order to approximate conditions that exist in the body.

On theoretical grounds Parsons (12) and L. J. Henderson (11) have concluded that the effect of oxygen on the CO_2-combining power of blood must depend on the amount of hemoglobin in the blood and the ratio of reduced hemoglobin to oxyhemoglobin. Christiansen, Douglas, and Haldane (9) and Joffe and Poulton (8) have presented experimental data that conform to this theory. It should be possible, then, to find an empirical mathematical expression for the effect of oxygen unsaturation on the level of the carbon dioxide absorption curve, the accuracy of which will depend on the accuracy of the data at our disposal. The simplest equation that will express the fact that the effect of oxygen unsaturation on the curve is dependent on the amount of reduced hemoglobin is

$$K \times \mathrm{Hb} = D$$

where K = a constant

Hb = the oxygen unsaturation of the blood expressed in volume per cent of oxygen

D = the change of level of the absorption curve as a result of the effect of oxygen unsaturation, expressed in volume per cent of carbon dioxide

Of course this formula cannot express the reaction accurately. K cannot be a simple constant because the curves of reduced and oxygenated blood meet at the origin. K must, therefore, have a value of zero at 0 mm. of CO_2 tension and must increase as the CO_2 tension rises. The value of K may, however, be sufficiently constant at CO_2 tensions that exist in the body to permit the use of such a simple equation.

As experimental data we have the carbon dioxide absorption curves of the blood of J. S. H. (Christiansen, Douglas, and Haldane) saturated with oxygen and 98 per cent reduced and the curves of the blood of J. (Joffe and Poulton) completely oxy-

genated and 90 per cent reduced. The hemoglobin values given for J. S. H. and J. are 100 and 101 per cent respectively, according to the Haldane scale. To these data we have applied the above equation and calculated values of K. The results are

TABLE IV.

Effect of Oxygen on the Carbon Dioxide Absorption Curve of Whole Blood, from Equation $K \times Hb = D$.

Subject.	CO_2 tension.	Observed value of D.	Value of K.
	mm. Hg		
J. S. H. (reduced blood 2 per cent saturated with oxygen. Hemoglobin 100 per cent.)	0	0	0
	10	5.5	0.303
	20	5.5	0.303
	30	5.6	0.309
	40	6.0	0.331
	50	6.2	0.342
	60	6.2	0.342
	70	6.6	0.364
	80	6.7	0.370
	90	7.0	0.368
J. (reduced blood 10 per cent saturated with oxygen. Hemoglobin 101 per cent.)	0	0	0
	10	4.5	0.268
	20	5.3	0.315
	30	5.6	0.333
	40	5.5	0.327
	50	5.5	0 327
	60	5.9	0.351
	70	6.5	0.386
	80	7.4	0.440
	90	8.0	0.476
Average values from 30 to 70 mm. inclusive.....		J. S. H.	0.337
		J.	0.345

shown in Table IV. It will be seen that the average values of K between 30 and 70 mm. of CO_2 tension are practically identical, averaging 0.34, and that the maximum deviation from this mean at these tensions is only about 10 per cent. This is within the

error of the method employed and a constant value of K can therefore be assumed for our purposes. We have applied this equation to our results in order to correct the arterial and venous CO_2 tensions observed for the effect of oxygen unsaturation. In practice a curve is drawn at the distance D above the curve of completely oxygenated blood and the corrected point is placed where the carbon dioxide content of the blood intersects this curve.

In the charts of experiments and in the tables of this paper the arterial and venous points are shown both in relation to the absorption curve of completely oxygenated blood and also after corrections have been made for oxygen unsaturation. The quantitation of the effect of oxygen unsaturation is, of course, based on insufficient data. If, however, the data of Haldane and of Joffe are correct and the value of K does vary by only 10 per cent, the maximum error in such a correction cannot be more than one-tenth of the variation produced by the change from the completely oxygenated to the completely reduced state. For a hemoglobin of 100 per cent the error would be 0.64 volume per cent, well within the limit of error of the analytical methods we have employed. Even a considerable error in the equation would make no distinguishable difference in the results.

Level of the Absorption Curve of Normal Resting Subjects.

Christiansen, Douglas, and Haldane (9), in 1914, studied the carbon dioxide absorption curve of two normal individuals (J. S. H. and C. G. D.) at rest, and during and after exercise. They also made a few observations on five other normal persons at rest. At about the same time Morawitz and Walker (16) made some observations on the carbon dioxide-combining power of whole blood, by an entirely different technique, and obtained almost identical results. Hasselbalch (10), in 1917, determined the curve of the normal subject, K. A. H. In 1918 Straub and Meier (5) published the results of a study of the absorption curves of 56 hospital patients in whom, they state, there was no reason to suspect any pathological change of the blood. Liljestrand and Lindhard (17), Krogh and Liljestrand (18), Joffe and Poulton (8), Parsons (12), Davies, Haldane, and Kennaway (19),

and Means, Bock, and Woodwell (4) have also given normal absorption curves.

In Fig. A are presented the limits of variation of the carbon dioxide absorption curves of normal resting individuals which we have been able to find in the literature, and those of three normal persons which we have determined. Some of these represent only single observations. Others are the results of repeated studies. Altogether observations on twenty-one normal persons appear, besides Straub's 56 hospital patients.

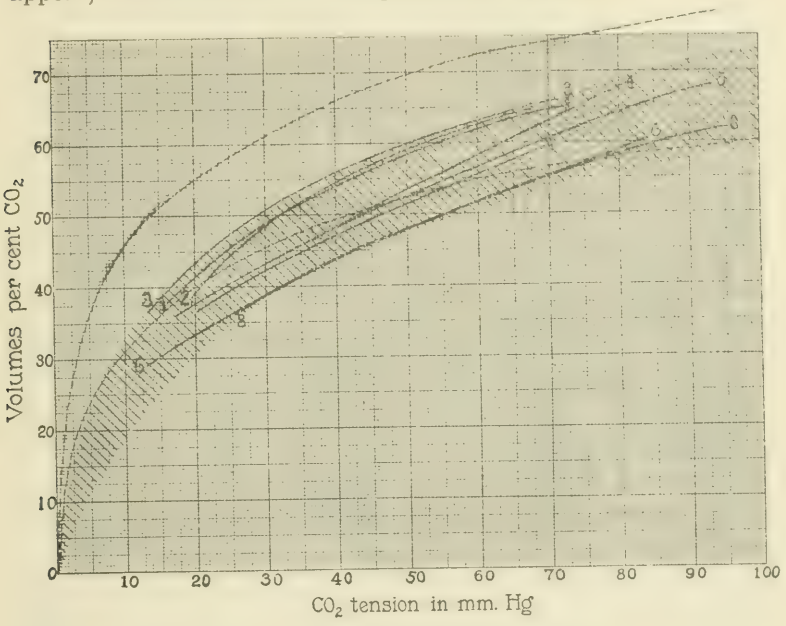

FIG. A. Absorption curves of three normal subjects.

1. J. P., Feb. 27, 1920.
2. " Mar. 5, 1920.
3. " " 12, 1920.
4. W. S. M., Feb. 13, 1920.
5. " May 21, 1920.
6. D. P. B., Mar. 26, 1920.
7. " " 29, 1920.
8. " May 14, 1920.

Shaded area shows the range of variation of the absorption curves of seventeen normal individuals, obtained from the literature. The area enclosed by broken lines represents the range of variation exhibited by Straub and Meier's 56 cases.

The methods employed are almost as numerous as the authors. Nevertheless, with the exception of Straub's highest figures, the agreement in the results of different observers is remarkably close. The normality of Straub's cases may reasonably be questioned and the data which he presents are not sufficient to permit analysis of his results. The simple statement that the clinical condition of these patients gave no reason to suspect any pathological change of the blood is not a sufficient characterization to warrant the assumption that they are normal subjects. As yet the study of the carbon dioxide absorption curve of whole blood has been too limited to permit one to say that pathological changes occur in certain restricted conditions, only. It seems better, then, to omit Straub's figures in discussing the limits of variation of the absorption curve in normal subjects. If this is done, it will be seen that the limits of variation of the eighteen cases reported by other observers are the same as those found in our three normal subjects. For the present, these must be considered the limits of range of the carbon dioxide absorption curve of normal resting subjects. It may be that further studies will reveal greater variations or that more careful investigation will prove that the extreme curves are due to some pathological or abnormal physiological condition not yet discovered.

The carbon dioxide content of blood is composed of two parts: (1) That portion which is present in simple solution and as H_2CO_3; (2) that portion which is present in chemical combination as bicarbonate. The amount of CO_2 in solution at any given temperature is dependent entirely on the tension of carbon dioxide to which the blood has been exposed, and can be calculated directly from this and the solubility coefficient. It has been shown by Bohr (20), L. J. Henderson (11), and more recently by Parsons (12) that practically all the chemically combined CO_2 must exist as bicarbonates. Henderson has also shown that the concentration of bicarbonates may be used as a measure of the alkali of the blood not bound by acids other than carbonic, without any significant error. If this is so, the alkali reserve of the blood must determine the height of the absorption curve.

Inspection of the curves discloses the fact that they vary considerably in shape and slope. In most cases these variations are minimal within the limits of CO_2 tension that are believed to

obtain in the arterial blood. If the curves of patients with severe anemia are omitted, the remainder will be found, with few exceptions, to maintain the same relative height within the limits 30 to 60 mm. In order to compare the heights of different absorption curves, it is necessary to study them at the same level. The ideal level from a theoretical standpoint is the one that conforms as nearly as possible to the conditions supposed to exist in the body; that is, where the absorption curve crosses the pH 7.35 line. In the lowest curves, however, this point lies at an extremely low carbon dioxide tension, occasionally below those tensions employed in the experimental work. The use of the point of intersection with the pH 7.35 line would, in these instances, demand extrapolation with the introduction of a considerable error. We have, therefore, chosen the point at which the absorption curve crosses the 40 mm. line. This point has been chosen because it is the generally accepted figure for average, normal alveolar CO_2 tension and because it has been rather generally employed by other investigators in the determination of the CO_2 capacity of whole blood and plasma. Except in certain pathological conditions which we shall discuss later, the differences in the results of the two methods (estimation of height at the 40 mm. line and at the pH 7.35 line) are insignificant. The height of the curve at either of these points may be considered to represent the alkali of the blood available for combination with CO_2 under conditions that exist in the body. This is expressed in terms of total carbon dioxide instead of carbon dioxide present as bicarbonate. The latter may be derived by subtracting 2.7 volumes per cent from the value given. The results obtained by others and by us, from both normal and pathological subjects, appear in Table V.

From these figures the height of the normal absorption curve at 40 mm. of CO_2 tension may be said to lie between 43 and 56 volumes per cent, with an average of about 50. The limits of the whole number of normal curves are practically the same as those found in our three normal subjects, if Straub's figures are omitted.

Christiansen, Douglas, and Haldane (9) found that, although the absorption curves of different individuals differed considerably in level, the absorption curve of any given individual was constant and quite characteristic in both height and shape.

TABLE V.

Height of the Absorption Curve at 40 Mm. CO_2 Tension.

Subject and condition.	CO_2
	vol. per cent
Christiansen, Douglas, and Haldane: 6 normal subjects; limits of variation	46.6 51.2
Morawitz and Walker: 1 normal subject; limits of variation	51.7 54.2
Hasselbalch: 1 normal subject, K. A. H	50.0
Krogh, Liljestrand, and Lindhard: 5 normal subjects; limits of variation	44.0 48.3
Joffe and Poulton: 1 normal subject, J	45.1
Parsons: 1 normal subject, T. R. P., Oct., 1917	51.9
July, 1918	46.7
Davies, Haldane, and Kennaway: 1 normal subject, J. B. S. H.	49.4
Means, Bock, and Woodwell: 2 normal subjects, M. N. W	51.1
J. H. M	50.9
Straub and Meier:* 56 hospital cases with presumably normal blood; limits of variation	49.5 65.6
J. P., normal subject, Feb. 27, 1920	53.9
Mar. 5, 1920	54.5
" 12, 1920	55.9
W. S. M., normal subject, Feb. 13, 1920	48.3
May 21, 1920	48.2
D. P. B., normal subject, Mar. 26, 1920	43.3
" 29, 1920	47.0
May 14, 1920	43.6

Summary.

	No. of cases.	CO_2 at 40 mm.		
		Maximum.	Minimum.	Average.
		vol. per cent	*vol. per cent*	*vol. per cent*
Other observers*	18	54.2	44.0	49.3
Subjects of this series	3	55.9	43.3	49.2
All normal subjects	21	55.9	43.3	49.3

* Straub and Meier's figures are omitted from this summary for reasons given in the text.

Our results seem to confirm this statement. The total variation in the height of the curve of J. P. (Case 1), determined three times in a period of 6 weeks, was only 2 volumes per cent. Two curves of W. S. M. (Case 2), obtained over 3 months apart, show even closer agreement. In the case of D. P. B. (Case 3), two curves at an interval of 6 weeks are almost identical. A third, taken 3 days after the first, lies about 4 volumes per cent higher. Christiansen, Douglas, and Haldane showed that exercise reduced the level of the curve. The variations that were found may have been due to a failure to establish proper resting metabolic conditions. The two curves of Case 3 that agree most exactly were obtained under standard conditions. The very close agreement of these curves derived from a considerable number of observations, scattered over a period of 2 months or more, can hardly be a matter of coincidence. It is also additional evidence that, for purposes of comparative study at least, the errors of the method are of no great importance.

The meaning of the differences in the height of the absorption curves of different individuals is not clear. That it is paralleled by no corresponding difference in the carbon dioxide tension of the alveolar air has been stated by Christiansen, Douglas, and Haldane. By a strange chance it happens that the absorption curves of Cases 1 and 3 are very different and lie respectively at the extreme upper and lower limits of the normal range. Both persons have been studied by a variety of respiratory methods and they have been found to differ in many respects. Some of these differences and their possible bearing on the height of the absorption curve will be pointed out later.

Carbon Dioxide Tension and the Hydrogen Ion Concentration of the Arterial Blood of Three Normal Subjects.

The carbon dioxide tension of the arterial blood of three normal persons (see Table VI, Columns 4 and 5; and Charts 1, 2, and 3[1]) was found to be 36 to 50.5 mm. of Hg uncorrected for oxygen unsaturation, 34.5 to 49 mm. after correction. This variation

[1] To facilitate the reference to charts and tables, the same numbering has been retained throughout tables, charts, and protocols. Thus Chart 1 refers to Case 1. Charts of general characteristics are lettered.

TABLE VI.

Results of the Study of Three Normal Subjects.

Subject.	Date.	Alveolar CO_2 tension.	Alveolar reaction.	Arterial CO_2 content.	Arterial CO_2 tension.		Arterial reaction.		Venous CO_2 content.	Venous CO_2 tension.		Venous reaction.		Difference between arterial and alveolar CO_2 tension.	Difference between venous and arterial CO_2 content.	Difference between venous and arterial CO_2 tension.	Difference between venous and arterial reaction.
					Uncorrected.	Corrected.	Uncorrected.	Corrected.		Uncorrected.	Corrected.	Uncorrected.	Corrected.				
		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
	192-	*mm. Hg*	*pH*	*vol. per cent*	*mm. Hg*	*mm. Hg*	*pH*	*pH*	*vol. per cent*	*mm Hg*	*mm. Hg*	*pH*	*pH*	*mm. Hg*	*vol. per cent*	*mm. Hg*	*pH*
1. J. P.	Feb. 27								57.4	47.5		7.33					
	Mar. 5								64.3	65.5		7.23					
	" 12	38.7	7.42	54.1	36.0	34.5	7.43	7.45	62.0	56.3		7.28		−4.2	7.9		
	May 19	36.0	7.42	54.1	39.0	38.7	7.40	7.40	55.6	42.0	39.5	7.37	7.40	2.7	1.5	0.8	0.00
2. W. S. M.	Feb. 13								64.1	72.0		7.19					
	May 21	35.9	7.35	50.9	47.0	45.0	7.28	7.30	59.4	67.5	52.5	7.18	7.30	9.1	8.5	7.5	0.00
3. D. P. B.	Mar. 26	38.5	7.29	45.5	45.0		7.25		53.4	65.0		7.15			7.9		
	" 29	37.6	7.33						57.5	65.0		7.18					
	May 14	37.4	7.30	47.9	50.5	49.0	7.22	7.23	56.2	72.0	58.5	7.12	7.22	11.6	8.3	9.5	0.01
Maximum		38.7	7.42	54.1	50.5	49.0	7.43	7.45	64.3	72.0	58.5	7.37	7.40	11.6	8.5	9.5	0.01
Minimum		35.9	7.29	45.5	36.0	34.5	7.22	7.23	53.4	42.0	39.5	7.12	7.22	(0.0)	1.5	0.8	0.00

did not bear a direct relation to the height of the corresponding absorption curves. The consequence is that our results indicate a considerable range of variation in the pH of normal arterial blood (see Table VI, Columns 6 and 7); from 7.22 to 7.43 uncorrected for oxygen unsaturation, 7.23 to 7.45 after correction. This is somewhat larger than the variation found by Michaelis (21) by direct electrometric titration in the venous blood of twelve normal resting persons, which was 7.28 to 7.43. As we shall show later the pH of venous blood is practically the same as that of arterial blood so that Michaelis' figures and ours are quite comparable. His average pH is 7.35, ours is 7.32, a very fair agreement. There are, as yet, no direct determinations of the pH of human arterial blood to be found in the literature. Most observers have relied, instead, on the values obtained from venous blood equilibrated with alveolar air.

Parsons' (12) objections to the use of the ratio of free to combined carbon dioxide as a measure of the hydrogen ion concentration of whole blood have been discussed above. If these objections are valid our figures cannot be interpreted as absolute values, but they must be very close to the true values. The differences of pH in the three individuals, moreover, are too great to be accounted for by errors in the method of calculation. Parsons considers the maximum error in calculation to be about 0.09; Hasselbalch (10) found the maximum error no greater than that of the method for determining CO_2, which he places at a difference of 0.04 in the pH. This may be increased somewhat by the error in the oxygen correction formula. A greater error, however, results if this correction is not made. Certainly it expresses the change in pH as in carbon dioxide qualitatively and, as we have shown, deals with a value of such small magnitude that the error must be minimal, probably not greater than 0.02 in pH. On the whole the maximum error should never exceed 0.06 and the average error must be nearer 0.02 to 0.03.

It is quite difficult to believe that the differences in pH found in J. P. (Case 1) and D. P. B. (Case 3) are due to errors in method, because repeated determinations revealed the same differences. Values of 7.22 and 7.25 were found in Case 3 at an interval of 6 weeks. In Case 1 in two experiments more than 2 months apart, arterial CO_2 contents were found to be identical. Unfortunately

on the second occasion the determination of the absorption curve failed. However, Case 1's absorption curve had been sufficiently well established by three other observations to warrant the assumption that the arterial CO_2 tension and the hydrogen ion concentration were the same on both occasions. In order to represent this second experiment graphically (see Chart 1) we have employed an absorption curve made up from the three previous experiments. Under these conditions the arterial pH of Case 1 on these two occasions was 7.40 and 7.45.

There is a variation in the pH of normal resting individuals of about 0.2, a little more than has been generally assumed. There seems to be a tendency for each individual to maintain his pH at a constant level. This is characteristic of the individual. We have other evidence that this must be so in the fact that the level of the carbon dioxide absorption curve and the level of the alveolar CO_2 tension, both determinants of the hydrogen ion concentration of the blood, are both constant in any given individual, although subject to a certain variation in different individuals.

If this is so one cannot talk in absolute terms of compensated or uncompensated acidosis or carbon dioxide retention from a single observation of the arterial pH under pathological or abnormal physiological conditions. If Case 1 normally maintains a pH above 7.4 in his arterial blood a pH of 7.30 would, in his case, indicate a retention of carbon dioxide or an uncompensated acidosis. But the same pH (7.30) would be normal for Case 2 and would mean an uncompensated alkalosis in the blood of Case 3. It is necessary to establish the normal pH level of an individual before one can accept as proof of uncompensated acidosis or alkalosis any values except such as lie beyond the limits of normal variation.

Relation of Alveolar and Arterial Carbon Dioxide Tension.

Hasselbalch (10) has shown that if the blood of an individual is exposed at body temperature to a mixture of CO_2 and air of the same CO_2 tension as that of the alveolar air of the subject, the pH of the blood will be found to vary only slightly about a mean of 7.35. This must mean that, in general, the alveolar carbon dioxide tension varies with the height of the absorption curve.

On the other hand, Christiansen, Douglas, and Haldane (9) make the statement that the alveolar CO_2 tension does not vary with the height of the absorption curve.

Table VII gives the calculated pH of blood equilibrated with an air-CO_2 mixture of the same CO_2 tension as that of the alveolar

TABLE VII.

pH of Blood Exposed to an Air-CO_2 Mixture of the Same CO_2 Tension as That of the Alveolar Air of the Individual from Whom Blood Was Removed.

(Values obtained by calculation from the absorption curve.)

Observer.	Subject.	Alveolar CO_2 tension.	Reaction.
		mm. Hg	*pH*
Christiansen, Douglas, and Haldane.	J. S. H.	40.8	7.35
	C. G. D.	38.5	7.35
	J. C.	35.0	7.35
	J. G. P.	40.2	7.35
Krogh and Lindhard.	A. K.		7.34
	J. L.		7.30
Means, Bock, and Woodwell.	J. H. M.	40.6	7.37
	M. N. W.	37.5	7.35
	1920		
The authors.	J. P.		
	Mar. 12	38.7	7.42
	May 19	36.0	7.42
	W. S. M.		
	May 21	35.9	7.35
	D. P. B.		
	Mar. 26	38.5	7.29
	" 29	37.6	7.33
	May 14	37.4	7.30
Average			7.35
Maximum			7.42
Minimum			7.29

air in the three normal persons of our series; four normal persons given by Christiansen, Douglas, and Haldane; A. K. and J. L. from data presented by Krogh and Liljestrand (18) and Krogh and Lindhard (22); and J. H. M. and M. N. W. from Means, Bock, and Woodwell (4). In the case of the subjects A. K. and

J. L. the absorption curves were taken from recently published work, while the figures for alveolar CO_2 tension employed were calculated from several series of observations reported in earlier studies. In all the other cases including our own, absorption curves and alveolar carbon dioxide were determined at the same time. We have calculated the pH by taking the point where the absorption curve of the individual crosses the line representing his alveolar CO_2 tension.

The average normal pH under these conditions is, as Hasselbalch found, 7.35. In spite of the statement of Christiansen, Douglas, and Haldane that they could find no exact relation between the height of the absorption curve and the alveolar carbon dioxide tension, their figures show a remarkable agreement. The difference between our conclusions and those of Christiansen, Douglas, and Haldane may be partially explained by unavoidable differences in the construction of the curves. Hasselbalch's calculations of the "alveolar pH" of J. S. H., C. G. D., and K. A. H. differ from ours by 0.01 and 0.02. This is about the error that should be expected in the construction of the most probable curve from a series of points that has an inherent error as great as that of methods for determining carbon dioxide in blood. The failure of Christiansen, Douglas, and Haldane to recognize the relation between the alveolar carbon dioxide tension and the height of the absorption curve may have been due also to the fact that this relation is not a linear function. They say that although the alveolar CO_2 of J. C. is 5 to 6 mm. lower than that of J. S. H. the corresponding absorption curves are almost indistinguishable. As we have reconstructed the curves from their data, that of J. C. appears to be 2.5 to 3.0 mm. lower than that of J. S. H. Owing to the slope of the pH lines and the dissociation curves, the difference in CO_2 tension between the points of intersection of these curves with the pH 7.35 line is about 6 mm.

The results of our experiments are not quite so satisfactory. Case 1 gives a pH of 7.42, while Case 3's is 7.29 to 7.33, with an average of 7.30. The fact that repeated observations gave identical results suggests that these relations are individual characteristics of the subjects under investigation. If we can accept the composite data for J. L. it is interesting to note that both his

alveolar CO_2 tension and absorption curve agree with those of Case 3, giving in both cases a low pH of only 7.30. In both, the absorption curves are so low that an alveolar CO_2 tension of 30 to 31 mm. would be required to produce a pH of 7.35. This is below the figures usually accepted for the lower limits of the normal range of alveolar CO_2 tension. Arguing in the same way, Case 1 would require an alveolar CO_2 tension of 45 mm. to bring his pH to the 7.35 line. Such an alveolar tension has never been observed in this subject although he has been studied for 5 years.

When the alveolar CO_2 tension is compared with that of the arterial blood (see Table VI, Column 12), the close agreement which has been generally assumed does not appear. From Charts 1, 2, and 3 it is found that, in Case 1, Experiment 1, the alveolar CO_2 tension is 4 mm. higher than that of the arterial blood; in the other two cases the alveolar tension is 6 to 11 mm. lower than that of the arterial blood.

The difference found in Case 1 can hardly be accepted at its face value. One might consider the findings in this case an indication that Krogh (22) and his followers were right in their statement that the values obtained by the Haldane method were too high. But every other observation here reported contradicts this. It is not easy to believe that there was an error in the collection or analysis of the alveolar samples. The subject is experienced in respiratory methods. Duplicate specimens checked perfectly. Not only is this true in this experiment, but in the experiment 2 months later values obtained for both alveolar CO_2 tension and arterial CO_2 content were almost identical with those of the earlier experiment. Finally the alveolar CO_2 was determined in conjunction with a respiratory experiment in which the dead space was calculated by the Haldane (3) formula. With the alveolar CO_2 as determined, a dead space of 130 cc. was obtained. If the alveolar CO_2 tension were assumed to be only 1.5 mm. below the arterial tension, the dead space would have to be as small as 75 cc. and the alveolar tension only 33 mm. Determinations of the dead space by Pearce's (23) method on the same subject gave a value of 130 cc. and his alveolar carbon dioxide tension has never been found as low as 35 mm. An alveolar CO_2 tension of 33 mm. would also, if placed on the dissociation

curve, give a pH of 7.47. The fault is, therefore, probably not in the determination of the alveolar CO_2 tension.

If the absorption curve were only 1.5 volumes per cent lower, the alveolar and arterial tensions would coincide. As we have pointed out, there is sufficient error in the method of determining the absorption curve to make it impossible to draw any conclusions from such small differences. The curve obtained on March 12 is perceptibly higher than three others obtained from the blood of Case 1 on other dates. If the average of all the curves of Case 1 is employed it is found that, in the experiments of March 12 and May 19, the alveolar CO_2 tension is respectively the same as and 3 mm. lower than the arterial tension. In Chart 1 such an average absorption curve has been used (Curve 2) in representing the experiment of May 19. For the experiment of March 12 (Curve 1), the absorption curve as actually determined on that day has been used. Curve 2, we believe, probably represents more nearly the actual relation between alveolar and arterial CO_2 tension in both experiments. In this case the two are, for practical purposes, identical.

The remaining cases are, however, not at all in keeping with the accepted theory which regards the alveolar CO_2 tension as a measure of the arterial tension. Krogh and Krogh (24) found that the alveolar CO_2 tension of rabbits was about 0.1 to 0.2 per cent lower than that of the arterial blood. Our experiments show a difference of 0.8 to 1.5 per cent in normal persons and, as we shall show, a much greater difference in some pathological conditions. Against the assumption that the alveolar CO_2 is in error the same arguments which were proposed in Case 1 may be advanced. In order to make the alveolar and arterial tensions agree by correcting the absorption curve the latter would have to be placed at least 2.5 volumes per cent higher. But in both these subjects repeated determinations of the absorption curve agreed perfectly. It is improbable that a systematic error would occur in four determinations on two subjects and fail altogether to appear in three experiments on a third. The difference between arterial and alveolar CO_2 tension in these cases seems to be a real one.

CO_2 Tension and Hydrogen Ion Concentration of Venous Blood and the Difference between Arterial and Venous Blood.

Results obtained from the analysis of venous blood are inherently less reliable than those obtained from arterial blood because the carbon dioxide and oxygen tension of the venous blood are subject to the influence of local conditions. The influence of venous stasis on both CO_2 content and CO_2-combining capacity has been brought out by Morawitz and Walker (16), as has the effect of exercise. Although it is possible to avoid artificial stasis by omitting the use of a tourniquet, it is impossible to control completely local changes in the blood flow or in the muscular activity of the arm. The fact that no simultaneous studies of arterial and venous blood from either normal or pathological subjects have given consistently satisfactory respiratory quotients is an indication that such factors are active even under the most carefully controlled conditions. Harrop's (25) blood respiratory quotients range from 1.81 to 0.62 in normal persons, 1.76 to 0.25 in cardiac subjects. Our own vary from 1.62 to 0.34. Arterial blood is not subject to the influence of local circulatory conditions and it is, therefore, probable that the chief source of error lies in the venous blood. It is obvious that, unless satisfactory quotients are obtained, the results cannot be considered to represent conditions that exist in the general circulation. Nor is it proper to accept as satisfactory isolated experiments in which satisfactory quotients are obtained. The method must be capable of returning such quotients with a certain degree of regularity in order to permit its use for the determination of the blood flow, venous CO_2 tension, and other similar characteristics in individual experiments. It may be possible, however, to draw general conclusions from the study of a considerable number of experiments.

In Table VI, Columns 9, 10, 11, 12, and 15, and Charts 1, 2, and 3 are given the CO_2 tension and the hydrogen ion concentration of the venous blood of the three normal subjects of our series with the difference in CO_2 tension between the arterial and venous blood. The CO_2 tension of venous blood was found to vary between 42 and 72 mm. uncorrected for oxygen unsaturation, 39.5 to 58.5 mm. after correction, with an average of 50.2

mm. The corresponding values for pH were 7.37 to 7.12 uncorrected, 7.40 to 7.22 corrected, with an average of 7.31. The difference between arterial and venous CO_2 tension was from 0.8 to 9.5 mm. corrected.

The range of variation of all these factors is very considerable. Especially noticeable is the very high venous carbon dioxide tension found in Cases 2 and 3. The first attempt to ascertain the venous carbon dioxide tension was made by Christiansen, Douglas, and Haldane (9) in 1914. Since then many other workers have proposed methods. All these methods are indirect and all depend on the same principle, the use of the lungs as a tonometer. The subject rebreathes a certain amount of air or some other gas mixture for a length of time less than that consumed by a single complete circulation of the blood. During this time the rebreathed air is supposed to attain equilibrium with the venous blood in the pulmonary circulation. From the CO_2 tension of the rebreathed mixture the CO_2 tension of the venous blood is calculated after a correction has been made for oxygen unsaturation. In order to find the arterial CO_2 tension the method of Haldane has been most commonly employed. By the use of these or similar methods all observers have found a difference between the arterial and venous carbon dioxide tension of from 4 to 7 mm. In some studies on the subjects J. P. (Case 1) and D. P. B. (Case 3) made with the Haldane method for arterial CO_2 tension and the Henderson (26) method for venous CO_2 tension we found the difference between the two to be from 2.7 to 7.0 mm. uncorrected for oxygen unsaturation, 1.6 to 4.2 mm. after correction. (The method of correction proposed by Christiansen, Douglas, and Haldane was used. In this 40 per cent of the total difference in CO_2 tension is subtracted as the effect of oxygen unsaturation.) The results obtained by our direct method and those obtained by the older, indirect methods are entirely incompatible. The new method gives more variable, but on the whole higher values.

It may be objected that it is not proper to criticize a method that aims to measure the carbon dioxide tension of the mixed venous blood in the pulmonary circulation on the basis of data obtained from the analysis of venous blood taken from an extremity. It may well be questioned whether the oxygen unsaturation

of the mixed venous blood of Cases 2 and 3 was as great as that found in the arm veins. The oxygen unsaturation in Case 3, Experiment 2, was 67.8 per cent and that of Case 2 was 76.7 per cent. (Lundsgaard (27), Stadie (2), and Harrop (25) found no normal subjects with a venous oxygen unsaturation of more than 40 per cent.) But this cannot explain the whole difference between the results of the direct and indirect methods. The marked oxygen unsaturation will be at least partially compensated by a change in the carbon dioxide-combining capacity of

TABLE VIII.

Difference between Arterial and Venous CO_2 Tension.

(Calculated from ten normal cases presented by Harrop.)

No.	Arterial CO_2 content.	Arterial O_2 saturation.	Venous CO_2 content.	Venous O_2 saturation.	Difference between arterial and venous CO_2 content.	Difference between arterial and venous CO_2 tension.	O_2 capacity.
	vol. per cent	*per cent*	*vol. per cent*	*per cent*	*vol. per cent*	*mm. Hg*	*vol. per cent*
1	51.8	97.5	57.2	74.3	5.4	8.8	23.7
2	54.7	100.0	56.7	84.9	2.0	2.1	17.2
3	52.9	94.3	55.9	64.4	3.0	6.0	16.3
4	46.5	96.3	51.7	67.1	5.2	8.0	20.6
5	44.8	95.1	48.3	80.8	3.5	6.5	18.7
6	49.7	96.0	54.6	61.6	4.9	6.3	20.6
7	48.1	96.3	52.2	75.0	4.1	7.8	14.4
8	50.6	97.6	58.7	64.0	8.1	13.3	24.7
9	53.3	94.4	60.4	73.5	7.1	14.5	18.9
10	44.6	99.0	50.9	61.8	6.3	8.5	21.2
Average					5.0	8.3	
Maximum					8.1	14.5	
Minimum					2.0	2.1	

the blood. Furthermore, it has already been shown that the air obtained by the Haldane method is not necessarily in equilibrium with the arterial blood, but may be as much as 9.5 mm. of CO_2 tension too low. In this case the values for the venous CO_2 tension obtained by the Henderson method must also be too low, because the two have been shown to differ by only 4 to 7 mm.

Three cases are hardly enough from which to come to very definite conclusions, but it is possible, for general purposes, at least, to use Harrop's figures. Harrop presents the carbon dioxide

content and oxygen unsaturation of both arterial and venous blood from ten normal persons. He gives no absorption curves so that it is impossible to estimate actual arterial and venous tensions from his data. We can, however, deduce with little error the difference between arterial and venous tension by assuming an average slope of 4 volumes per cent of CO_2 for each 10 mm. change in CO_2 tension at tensions that exist in the body. (The variations observed between 30 and 80 mm. are 5.75 to 3.53 volumes per cent per 10 mm., the curves gradually approaching the horizontal as the tension increases.) Assuming such an average slope and employing our formula for correction for oxygen unsaturation we arrive at the results shown in Table VIII. The difference between arterial and venous CO_2 content is from 2.0 to 8.1 volumes per cent, with an average of 5.0 volumes per cent. The difference in tension produced by such a difference in content is 5.0 to 20.0 mm. of Hg uncorrected for oxygen unsaturation, or 2.1 to 14.5 mm. after correction, with an average of 8.4 mm. These values are of essentially the same magnitude as those we obtained.

DISCUSSION.

It has been shown that the alveolar CO_2 tension varies with the height of the absorption curve in such a way that if blood is brought into equilibrium at 37.5°C. with an air-CO_2 mixture of the same CO_2 tension as that of the alveolar air of the subject from whom the blood was obtained, the hydrogen ion concentration of the blood so treated will be found to vary between pH 7.40 and 7.30, with an average of 7.35. At the same time the hydrogen ion concentration of the arterial blood shows a variation twice as great, from pH 7.45 to 7.23. The alveolar and arterial tensions are not identical.

As has been pointed out (28), the alveolar CO_2 tension can be considered from two points of view: (1) As a measure of the arterial CO_2 tension; (2) as an indication of the functional condition of the respiratory mechanism. As a measure of the arterial CO_2 tension it seems to be of less value than it has been commonly considered. But this detracts nothing from its value as an indication of the functional state of the respiratory mechanism. It still remains the effective respiratory air. The real

significance of the fact that the CO_2 tension of this "effective air" varies with the height of the absorption curve may be better appreciated if it is stated in terms of effective ventilation. In this sense it is the portion of the respired air which effects the exchange of gases between the blood and the outside air. From the standpoint of carbon dioxide it is the portion of the expired air that effects the necessary CO_2 elimination. A knowledge of the carbon dioxide output and the alveolar carbon dioxide tension is all that is necessary, therefore, to permit the calculation of the effective ventilation by the formula

$$\frac{\text{Cc. } CO_2 \text{ expired per minute} \times 100}{\text{Per cent } CO_2 \text{ in alveolar air}} = \text{Effective minute volume}^2$$

As the cc. CO_2 expired per minute under resting conditions is comparatively constant, one can say with sufficient accuracy for our purposes that the effective ventilation varies inversely as the alveolar CO_2 per cent. But as the latter varies with the height of the absorption curve, it follows that the effective ventilation must vary inversely as the height of the absorption curve.

This can have but one result: it must tend to maintain the hydrogen ion concentration of the blood at a constant level. Why, then, do we find the variations in arterial pH so great? Because of the slope of the absorption curve small changes in the carbon dioxide content of the blood produce relatively large changes in the carbon dioxide tension. The carbon dioxide content of the blood must be largely dependent upon the carbon dioxide production in the body and must fluctuate with the least change in activity. It would be impossible for the alveolar air to follow these changes immediately and accurately without the destruction of the rhythmicity of respiratory activity. In this case an instantaneous cross-section of the respiratory system such as is presented in these experiments might show considerable temporary disturbances of normal relations. It is inevitable also that these should be most striking in that element of the system which is susceptible to the most rapid changes, the blood; and

[2] The principle on which this formula depends has been employed for estimation of effective ventilation by Campbell, Douglas, Haldane, and Hobson (Campbell, J. M. H., Douglas, C. G., Haldane, J. S., and Hobson, F. G., *J. Physiol.*, 1913, xlvi, 301) and Haggard and Henderson (1).

least evident in the slowest moving portion of the system, the alveolar air.

This would be an entirely satisfactory explanation of temporary differences between alveolar and arterial tension found in single observations; *e.g.*, Case 2. But in Case 3 this difference was found on two different occasions and therefore appeared to be a constant and distinctive characteristic of the subject. The pressure difference necessary to effect the passage of carbon dioxide from the blood in the lungs into the alveolar air is greater than has been supposed, in this case at least. This may mean that the invasion coefficient for CO_2 is not what it has been supposed. It more probably means that the term "alveolar air" has not an exact anatomical significance and that the respiratory air, even from the deeper portions of the lungs, is not of uniform composition and is not all in close communication with the blood in the pulmonary circulation. It may indicate that even in normal persons part of the blood passes through unventilated or incompletely ventilated portions of the lung.

There must be material individual differences in reaction. If the charts of Case 1 and Case 3 (Charts 1 and 3) are compared closely, it is at once evident that every element of the latter lies considerably to the right of the corresponding element of the former. The mechanism seems to be set at a different point. One might say that the respiratory system of Case 3 was relatively insensible to acid. In substantiation of this idea it was found in some previous experiments of a different sort that this subject presented a far greater tolerance to carbon dioxide in rebreathing experiments than did Case 1. The latter exhibited marked distress when the CO_2 of the inspired air rose to about 8 per cent. At this point his respiratory rate became extremely rapid and his tidal air was maximal. At 8.5 per cent of CO_2, Case 3 had increased his tidal air to a maximum, but his respiratory rate was almost unchanged and he experienced only moderate discomfort.

Although it has been demonstrated that the difference in CO_2 tension between arterial and venous blood is very variable and may be larger than was indicated by indirect methods, the corresponding difference in pH is astonishingly small. In Case 3, May 14 (Chart 3, Experiment 2), the difference in carbon dioxide

tension even after correction for oxygen unsaturation was 9.5 mm. of Hg. The corresponding difference in pH was only 0.01. This is, of course, partly due to the slope of the absorption curve but far more to the effect of oxygen and the slope of the pH lines. When arterial blood is changed to venous blood the carbon dioxide increase must bear a definite relation to the oxygen reduction. It appears from the charts that, in persons with a normal hemoglobin, these two factors very nearly equalize one another. That the effect of oxygen on the carbon dioxide absorption curve should tend to diminish the difference in hydrogen ion concentration between arterial and venous blood has already been pointed out by Christiansen, Douglas, and Haldane (9), Hasselbalch (10), Parsons (12), and L. J. Henderson (11). The quantitative relations of the reaction have not been previously established.

By comparison of the charts of Cases 1 and 3 it appears that the ability to maintain the hydrogen ion concentration unchanged in the face of alterations in the carbon dioxide is a variable one. Thus Case 1, May 19 (Chart 1, Curve 2), for a change of 0.8 mm. in CO_2 tension shows no change in the pH; while Case 3, May 14 (Chart 3, Experiment 2), for 9.5 mm. of CO_2 tension shows a change of only 0.01 in pH. This is partly due to the fact that the pH lines, passing through the origin, become more nearly horizontal as the pH diminishes. In order to compensate for large carbon dioxide changes it is of advantage to work at a low pH, or, in terms of the charts, at the right of the chart. This advantage is further increased by the fact that the curves more nearly approach the horizontal as they pass to the right, so that the effect of oxygen is much more marked. This may be a further explanation of the greater tolerance of Case 3 for carbon dioxide in the inspired air.

Haggard and Henderson (14) have taken the position that oxygen is without effect on the carbon dioxide absorption curve of blood and have placed their arterial points accordingly. The close agreement of the values obtained by Michaelis (21) on venous blood, by Hasselbalch (10) on blood equilibrated with alveolar CO_2, and by us on arterial blood is perfectly incomprehensible if Henderson is right. The average difference in carbon dioxide content of arterial and venous blood of normal resting subjects as determined by Harrop (25) and the authors from thirteen persons

is 5.5 volumes per cent. This would give a difference of 0.2 in pH on any normal curve. If the arterial pH is 7.4 to 7.2, the venous pH would then have to be 7.2 to 7.0, far below any values actually found.

Miscellaneous Cases.

Although our interest lay primarily in the study of cardiac decompensation and anemia, two patients with other conditions were subjected to complete experiments. As they belong to neither of our special pathological groups they are reported here. One of these had a moderate polycythemia without splenomegaly, Case 4 (Chart 4). This was not sufficient to alter his absorption curve in a very striking manner, although it shows a slope slightly in excess of the normal. In other respects his chart is indistinguishable from that of a normal person. Again we may note a difference of 10 mm. between the alveolar and arterial carbon dioxide tensions, in spite of the absence of signs of pulmonary and cardiac disease.

Chart 5 is obtained from a patient with advanced chronic nephritis and hypertension. His curve lies at the lowest limit of the normal range and may indicate some reduction of the alkali of the blood. In spite of Cheyne-Stokes respirations there is no evidence of any retention of carbon dioxide, as the arterial pH is 7.37. The arterial-venous difference in carbon dioxide is surprisingly small.

In both cases arterial and venous pH are identical.

SUMMARY AND CONCLUSIONS.

The carbon dioxide absorption curve of human blood from three normal subjects has been determined.

The limits of variation of curves obtained from the blood of normal persons agree with those reported by previous observers. The limits of the carbon dioxide capacity of normal blood at 40 mm. of CO_2 tension and 37.5°C. are 43 and 56 volumes per cent with an average of 49 volumes per cent. Curves of different individuals vary in height and to a lesser extent in pitch. The curve of any given individual is quite characteristic and remains constant over a considerable period of time, as has been previously demonstrated by Christiansen, Douglas, and Haldane.

A direct method for the estimation of the arterial and venous carbon dioxide tension of human blood is described. It has been employed on three normal subjects at rest. The hydrogen ion concentration of arterial and venous blood has been calculated by means of the H_2CO_3:$BHCO_3$ ratio. At the same time the alveolar carbon dioxide tension has been determined by the method of Haldane and Priestley and compared with the arterial carbon dioxide tension found by the direct method.

1. The alveolar carbon dioxide varies, in general, with the height of the absorption curve in such a way that the hydrogen ion concentration of the blood of an individual equilibrated with an air-CO_2 mixture of the same CO_2 tension as that of his alveolar air, will fall between the limits of pH 7.42 and 7.29.

2. Although the relation of alveolar CO_2 tension to height of absorption curve shows this variation in a study of a number of persons, it is constant and characteristic for any one individual.

3. The arterial carbon dioxide tension shows about twice as great a range of variation in relation to the height of the absorption curve. In consequence the arterial pH varies from 7.23 to 7.45. The pH of any one individual is constant and characteristic.

4. The alveolar CO_2 tension is not always the same as the CO_2 tension of the arterial blood. It may be as much as 10 or 11 mm. lower.

5. The carbon dioxide tension of venous blood from an arm vein is higher than the values which have been obtained by the rebreathing methods for mixed venous blood. The difference between arterial and venous tension is variable. It averaged 6 mm. but may be as low as 0.8 mm. or as high as 10 mm. Calculations based on the figures for CO_2 content of arterial and venous blood given by Harrop substantiate our results.

6. Values have been corrected for the effect of oxygen unsaturation on the carbon dioxide-combining capacity of the blood. An empirical equation for such correction is presented.

7. In spite of the large difference between arterial and venous carbon dioxide tension, the pH of the two is almost identical largely because of the effect of oxygen on the carbon dioxide-combining power of the blood. It is pointed out that unless such a mechanism were present to reduce fluctuations in hydrogen ion concentration, the values found by other observers for the pH of venous blood would be impossible.

BIBLIOGRAPHY.

1. Haggard, H. W., and Henderson, Y., *J. Biol. Chem.*, 1919, xxxix, 163.
2. Stadie, W. C., *J. Exp. Med.*, 1919, xxx, 215.
3. Haldane, J. S., and Priestley, J. G., *J. Physiol.*, 1904–05, xxxii, 225.
4. Means, J. H., Bock, A. V., and Woodwell, M. N., *J. Exp. Med.*, 1921, xxxiii, 201.
5. Straub, H., and Meier, K., *Biochem. Z.*, 1918, lxxxix, 156; *Deutsch. Arch. klin. Med.*, 1919, cxxix, 54.
6. Van Slyke, D. D., *J. Biol. Chem.*, 1917, xxx, 347.
7. de Corral, J. M., *Biochem. Z.*, 1915, lxxii, 1.
8. Joffe, J., and Poulton, E. P., *J. Physiol.*, 1920–21, liv, 129.
9. Christiansen, J., Douglas, C. G., and Haldane, J. S., *J. Physiol.*, 1914, xlviii, 244.
10. Hasselbalch, K. A., *Biochem. Z.*, 1917, lxxviii, 112. Hasselbalch, K. A., and Lundsgaard, C., *Biochem. Z.*, 1912, xxxviii, 77. Hasselbalch, K. A., and Warburg, E. J., *Biochem. Z.*, 1918, lxxxvi, 410.
11. Henderson, L. J., *Am. J. Physiol.*, 1908, xxi, 427.
12. Parsons, T. R., *J. Physiol.*, 1917, li, 440; 1919–20, liii, 42, 340.
13. Henderson, L. J., *J. Biol. Chem.*, 1920, xli, 401.
14. Haggard, H. W., and Henderson, Y., *J. Biol. Chem.*, 1920–21, xlv, 215.
15. Van Slyke, D. D., and Cullen, G. E., *J. Biol. Chem.*, 1917, xxx, 289.
16. Morawitz, P., and Walker, J. C., *Biochem. Z.*, 1914, lx, 395.
17. Liljestrand, G., and Lindhard, J., *J. Physiol.*, 1919–20, liii, 420.
18. Krogh, A., and Liljestrand, G., *Biochem. Z.*, 1920, civ, 300.
19. Davies, H. W., Haldane, J. B. S., and Kennaway, E. L., *J. Physiol.* 1920–21, liv, 32.
20. Bohr, C., in Nagel, W., Handbuch der Physiologie des Menschen, Braunschweig, 1909, i, 55.
21. Michaelis, L., Die Wasserstoffionenkonzentration, Berlin, 1914.
22. Krogh, A., and Lindhard, J., *J. Physiol.*, 1917, li, 59.
23. Pearce, R. G., *Am. J. Physiol.*, 1917, xliii, 73.
24. Krogh, A., and Krogh, M., *Skand. Arch. Physiol.*, 1909–10, xxiii, 179.
25. Harrop, G. A., Jr., *J. Exp. Med.*, 1919, xxx, 241.
26. Henderson, Y., *J. Biol. Chem.*, 1917, xxxii, 325.
27. Lundsgaard, C., *J. Biol. Chem.*, 1918, xxxiii, 133.
28. Peters, J. P., Jr., and Barr, D. P., *Am. J. Physiol.*, 1920–21, liv, 307, 335. Barr, D. P., and Peters, J. P., Jr., *Am. J. Physiol.*, 1920–21, liv, 345.

EXPLANATION OF CHARTS.

In all charts the ordinates represent the total carbon dioxide content of the blood, expressed in volumes per cent of gas, dry, at 0°, 760 mm. The abscissa represents carbon dioxide tension in mm. of mercury.

That portion of the absorption curve which was experimentally determined is indicated by a solid black line. Extrapolated portions of the curve are indicated by broken lines. In all the pathological cases the limits of variation of the normal absorption curve are shown enclosed by broken lines.

The pH values are calculated by means of the formula of Y. Henderson.

The arterial points are shown as solid circles. The values uncorrected for oxygen are marked A; the corrected values are marked A'. The venous points are indicated by solid squares. The uncorrected points are marked V, the corrected points V'.

The alveolar carbon dioxide tension is indicated in those instances in which it was obtained. The plasma carbon dioxide-combining capacity is also shown in some cases, expressed in terms of the alveolar carbon dioxide tension with which it should agree in normal persons, according to Van Slyke. The case numbers and chart numbers follow the numbering of the protocols.

CHART 1.

Case 1. J. P., normal subject.

Experiment 1. Feb. 27, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	73.7	47.5	15.9
CO_2, *vol. per cent*	64.9	57.7	37.1
	66.5	56.9	37.6

CO_2 content of venous blood, *vol. per cent* 57.1
57.5

Experiment 2. Mar. 5.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	20.3	40.5	65.6
CO_2, *vol. per cent*	39.1	53.7	64.0
	40.0	56.3	

CO_2 content of venous blood, *vol. per cent* 64.3
64.3

Experiment 3. Mar. 12.

Minute volume of respirations, *cc* 7,150
Tidal air 520 cc. Respirations per min 13.7
CO_2 in expired air 4.29 per cent. CO_2 output per min., *cc.* 306
Alveolar CO_2 before determining minute volume, *mm* 41.4
" CO_2 " arterial puncture, *mm* 39.6
" CO_2 after " " " 37.7

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	74.1	47.6	12.2
CO_2, *vol. per cent*	64.3	58.7	34.7
	67.4		

CO_2 content of arterial blood, *vol. per cent* 54.0
54.2

CO_2 " " venous " " " " 62.2
61.7

Difference between arterial and venous CO_2 content, *vol. per cent* 7.9
CO_2 capacity of venous plasma (50.2 mm. Hg), *vol. per cent* 73.0
O_2 content of arterial blood, *vol. per cent* 19.8
O_2 capacity of blood, *vol. per cent* 22.5
O_2 saturation of arterial blood, *per cent* 88

Experiment 4. May 19.

Alveolar CO_2 before arterial puncture, *mm* 38.2
" CO_2 after " " " 37.2
37.0

CO_2 content of arterial blood, *vol. per cent* 54.4
53.7

CO_2 " " venous " " " " 55.7
55.5

Difference between arterial and venous CO_2, *vol. per cent.*	1.5
O_2 capacity of blood, *vol. per cent*	22.1
	22.5
O_2 content of arterial blood, *vol. per cent*	21.5
O_2 " " venous " " " "	18.3
	18.7
O_2 consumption, *vol. per cent*	3.0
O_2 saturation of arterial blood, *per cent*	96
O_2 " " venous " " "	83
Respiratory quotient of blood	0.50

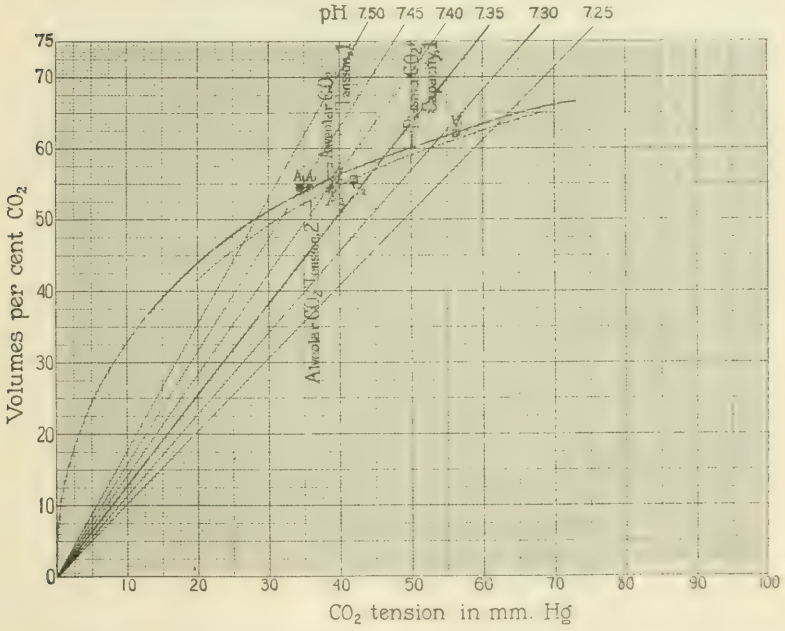
pH 7.50 7.45 7.40 7.35 7.30 7.25
Volumes per cent CO_2
CO_2 tension in mm. Hg
Alveolar CO_2 Tension 1
Alveolar CO_2 Tension 2
Curve 1
Curve 2

CHART 1. 1. Experiment of Mar. 12.

2. Experiment of May 19. The absorption curve was not determined with this experiment. The absorption curve employed is the average of three determinations made on J. P. on different occasions.

CHART 2.

Case 2. W. S. M. Normal subject.
Experiment 1. Feb. 13, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	13.7	80.6	52.1
CO_2, *vol. per cent*	32.5	66.6	54.5
	35.5	70.0	

CO_2 content of venous blood, *vol. per cent* 63.8
64.3

Experiment 2. May 21. The arterial puncture was rendered difficult by an arterial anomaly. Three punctures were necessary before blood was obtained, causing considerable pain and discomfort. The arm was held rigid during the venous puncture.

Alveolar CO_2 before arterial puncture, *mm* 33.5
" CO_2 after " " " 34.3
36.7

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	94.0	60.2	36.3
CO_2, *vol. per cent*	68.1	56.6	47.2
	68.3		46.1

CO_2 content of arterial blood, *vol. per cent* 50.5
51.3
CO_2 " " venous " " " " 58.9
59.9
Difference between arterial and venous CO_2, *vol. per cent* ... 8.5
O_2 capacity of blood, *vol. per cent* 24.9
O_2 content of arterial blood, *vol. per cent* 21.9
O_2 " " venous " " " " 5.8
O_2 consumption of blood, *vol. per cent* 16.1
O_2 saturation of arterial blood, *per cent* 88
O_2 " " venous " " " 23
Respiratory quotient of blood 0.53

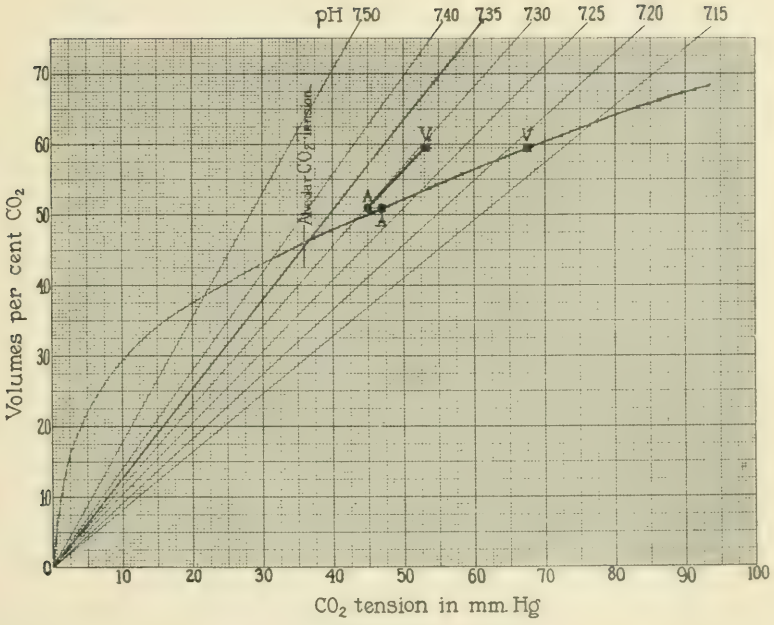
pH 7.50
7.40
7.35
7.30
7.25
7.20
7.15
Alveolar CO2 tension
V
V
A
A
Volumes per cent CO2
0
10
20
30
40
50
60
70
80
90
100
CO2 tension in mm. Hg

CHART 2.

CHART 3.

Case 3. D. P. B. Normal subject.

Experiment 1. Mar. 26, 1920.

Alveolar CO_2 before arterial puncture, *mm* 38.5
38.8

" CO_2 after " " " 38.2

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	85.1	45.0	8.9
CO_2, *vol. per cent*	60.9	45.4	25.1
	61.3		26.0

CO_2 content of arterial blood, *vol. per cent* 45.1
45.9

CO_2 " " venous " " " " 53.1
53.6

Difference between arterial and venous CO_2, *vol. per cent* ... 7.8

CO_2 capacity of venous plasma (43.3 mm. Hg) " " " ... 62.9

Experiment 2. Mar. 29.

Alveolar CO_2 before venous puncture, *mm* 39.5
38.7

" CO_2 after " " " 36.0

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	70.1	41.5	20.1
CO_2, *vol. per cent*	59.9	45.2	36.7
	59.9	47.0	37.9

CO_2 content of venous blood, *vol. per cent* 57.7
57.3

CO_2 capacity of venous plasma (45.4 mm. Hg), *vol. per cent*.. 65.9

Experiment 3. May 14.

Alveolar CO_2 after arterial puncture, *mm* 37.4

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	45.2	23.5	96.0
CO_2, *vol. per cent*	45.3	35.0	61.7
	46.1	35.2	61.9

CO_2 content of arterial blood, *vol. per cent* 47.6
48.1

CO_2 " " venous " " " " 56.2
56.2

Difference between arterial and venous CO_2, *vol. per cent* ... 8.3

O_2 capacity of blood, *vol. per cent* 21.4

O_2 content of arterial blood, *vol. per cent* 19.3

O_2 " " venous " " " " 6.9

O_2 consumption, *vol. per cent* 12.4

O_2 saturation of arterial blood, *per cent* 90

O_2 " " venous " " " 32

Respiratory quotient of blood 0.67

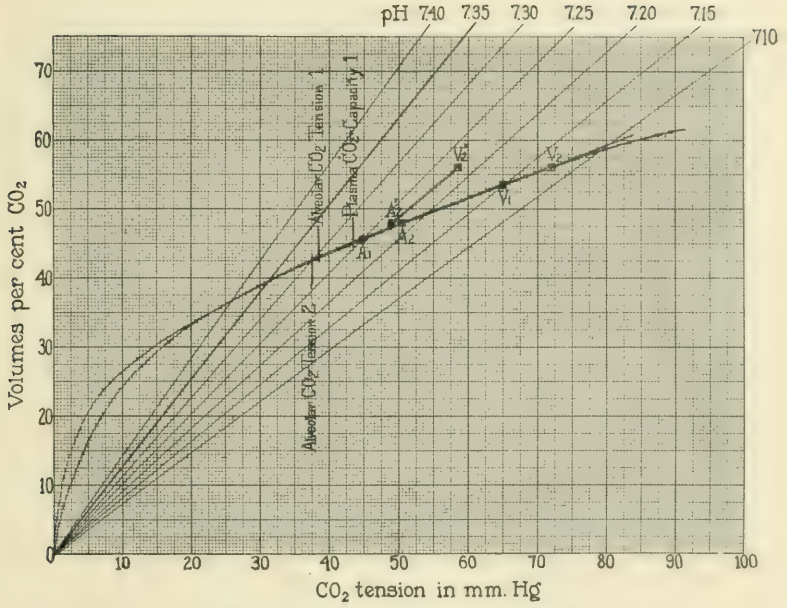

CHART 3. 1. Experiment of Mar. 26.
2. Experiment of May 14.

CHART 4.

Case 4. H. R. Polycythemia. Male, age 36 years. Russian, fireman. History of attacks of dizziness and fainting at intervals for 18 months. For 1 year slight dyspnea on exertion and sharp pains in muscles. Feels lethargic and sleepy in the day time, but restless and wakeful at night. Has to get up two or three times every night to urinate.

Very large man with florid complexion, whose respirations seem somewhat labored. Does not appear to be ill and lies quietly in bed. Tonsils very large and ragged. Lungs clear.

Blood Wassermann negative. Urine negative on two examinations. Fasting blood sugar 130 mg. per 100 cc. 2 hours after 100 gm. glucose by mouth, the blood sugar was still 235 mg. per 100 cc. and he excreted sugar continuously for 24 hours.

Several blood counts gave red blood cell figures varying from 7,800,000 to 8,100,000 in both venous and finger blood. Temperature and pulse normal.

Experiment 1. Apr. 12, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	76.5	67.9	53.6	5.4
CO_2, *vol. per cent*	60.6	56.8	50.3	20.7
		58.6		

O_2 capacity of blood, *vol. per cent* 23.4

Experiment 2. Apr. 28. Has been on a low calory diet with low carbohydrate for 1 week. Respirations quieter than at last observation. Slight cyanosis of finger-tips.

Alveolar CO_2 before arterial puncture, *mm* 34.7
35.9
" CO_2 after " " " 33.6

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	50.2	18.5
CO_2, *vol. per cent*	54.6	31.8
	52.8	32.9

CO_2 content of arterial blood, *vol. per cent* 50.9
49.9
CO_2 " " venous " " " " 60.5
59.9

Difference between arterial and venous CO_2, *vol. per cent* ... 9.8
CO_2 capacity of venous plasma (47.7 mm. Hg), *vol. per cent.* 68.6
O_2 " " blood, *vol. per cent* 23.9
O_2 content of arterial blood, *vol. per cent* 22.6
O_2 " " venous " " " " 8.1
O_2 consumption, *vol. per cent* 14.5
O_2 saturation of arterial blood, *per cent* 95
O_2 " " venous " " " 38
Respiratory quotient of blood 0.68

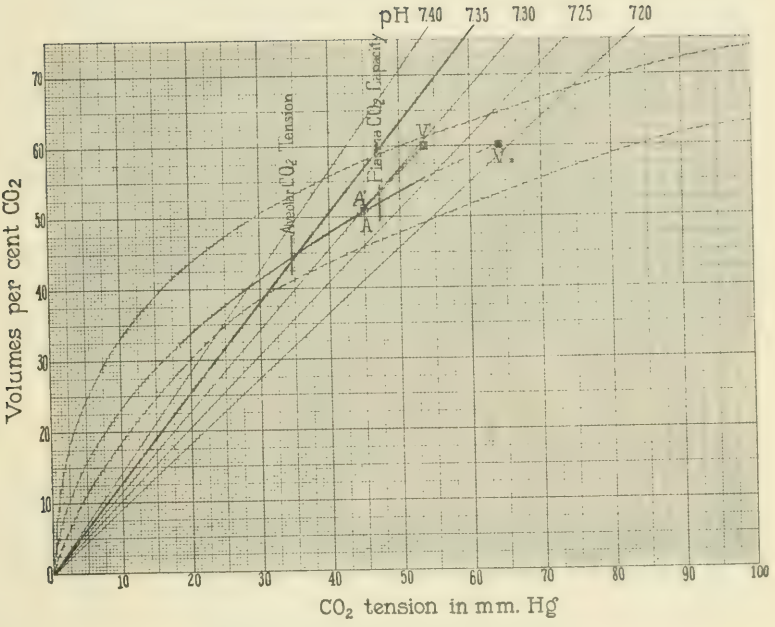

CHART 4. Experiment of Apr. 28.

Chart 5.

Case 5. H. G. Chronic cardionephritic. Male, age 60 years, real estate agent. Looks chronically ill. Quite pale. Cheyne-Stokes breathing with very short periods of apnea. Spastic paralysis of left leg and weakness of muscles of right side of face. Somewhat irrational with loss of emotional control.

Fine râles over left lung at end of inspiration. Heart enlarged to the left, with diastolic murmur over the aortic area and at the apex. Frequent extra systoles. Pulse 64 to 84. Blood pressure: systolic 160, diastolic 90 (has been above 200). Urine shows trace of albumin, no casts. Specific gravity 1.008. Non-protein nitrogen of blood 53 mg. per 100 cc.

Blood count: 4,700,000 red blood cells.

Experiment 1. May 24, 1920. Moderate cyanosis of face and hands. Some dyspnea with Cheyne-Stokes breathing. Arterial blood withdrawn during about equal portions of dyspneic and apneic periods.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	82.1	28.6	45.3
CO_2, *vol. per cent*	54.8	38.9	46.9
	53.5	38.3	48.8

CO_2 content of arterial blood, *vol. per cent*	40.4
	41.4
CO_2 " " venous " " " "	42.7
	44.0
Difference between arterial and venous CO_2, *vol. per cent*	2.4
CO_2 capacity of venous plasma (36.6 mm. Hg), *vol. per cent*	53.3
O_2 " " blood, *vol. per cent*	16.4
O_2 content of arterial blood, *vol. per cent*	13.8
O_2 " " venous " " " "	9.3
O_2 consumption of blood, *vol. per cent*	4.5
O_2 saturation of arterial blood, *per cent*	84
O_2 " " venous " " "	57
Respiratory quotient of blood	0.53

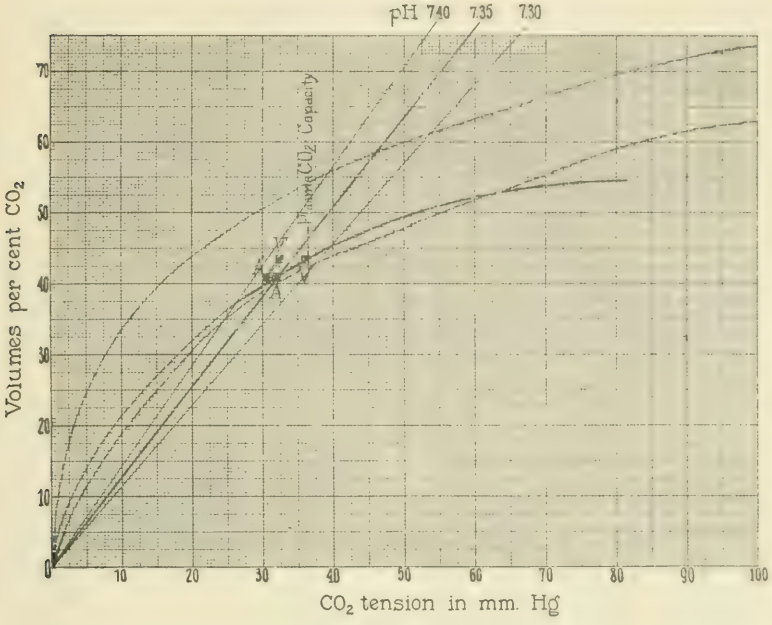

CHART 5.

Miscellaneous Protocols.

Case 21. Jno. K. Diabetes mellitus. Male, age 21 years. Diabetes mellitus of about 7 months duration, moderately severe. Admitted Apr. 5, 1920, with blood sugar of 256 mg. per 100 cc. and marked glycosuria. Emaciated. Skin dry. Cheeks flushed. No dyspnea nor hyperpnea. No cyanosis. Heart and lungs negative to physical examination.

Experiment 1. Apr. 6.

Alveolar CO_2, *mm*..... 30.0
29.7
30.8

CO_2 absorption curve:

CO_2 tension, *mm. Hg*.....	82.9	68.1	32.7	14.1
CO_2, *vol. per cent*.....	58.2	53.1	37.6	27.5

CO_2 capacity of venous plasma (34.9 mm. Hg), *vol. per cent*.. 50.7

O_2 " " blood, *vol. per cent*..... 19.2

Case 22. I. M. Diabetes mellitus. Male, age 52 years, married, suit presser. Diabetes of about 7 months duration, rather mild. Well nourished and developed. No dyspnea or hyperpnea. No cyanosis. Blood sugar 202 mg. per 100 cc. Heart negative. Blood pressure: systolic 140,

diastolic 88. Lungs show few, scattered, moist râles. Discharged from hospital sugar-free on diet containing 1,650 calories.

Experiment 1. Apr. 14, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	71.1	18.1	58.4
CO_2, *vol. per cent*	56.1	29.4	51.1
	59.0	32.3	

CO_2 capacity of venous plasma (40.9 mm. Hg), *vol. per cent.* 59.5

O_2 " " blood, *vol. per cent* 24.4

Case 23. I. S. Diabetes mellitus. Male, age 42 years, married, cutter. Diabetes of moderate severity for 2½ years. Emaciated, drowsy. No visible signs of dyspnea or hyperpnea. No cyanosis. Lungs and heart negative. Slight pitting edema of the ankles. Blood sugar 274 mg. per 100 cc. Urine shows considerable sugar and acetone. Temperature and pulse normal.

Experiment 1. Mar. 31, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	76.0	49.3	28.3
CO_2, *vol. per cent*	62.0	49.3	39.5
		48.0	38.5

CO_2 capacity of venous plasma (43.7 mm. Hg), *vol. per cent.* 63.5

O_2 " " " blood, *vol. per cent* 17.9

18.2

Case 24. D. A. Diabetes mellitus with vulvar abscess. Old woman with senile dementia and diabetes of long standing, complicated by an extensive cellulitis of the vulva. Breathing quietly. Slightly cyanotic. Blood sugar 333 mg. per 100 cc.

Experiment 1.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	78.4	42.3	17.8
CO_2, *vol. per cent*	61.6	42.4	27.4
	61.5	44.0	28.9

CO_2 content of venous blood, *vol. per cent* 56.8

57.5

CO_2 capacity of venous plasma (46.8 mm. Hg), *vol. per cent.* 68.0

O_2 " " blood, *vol. per cent* 23.8

Case 25. E. C. Emphysema with slight cardiac decompensation.

Experiment 1.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	85.2	25.5
CO_2, *vol. per cent*	70.2	44.5
	68.8	44.6

O_2 capacity of blood, *vol. per cent* 22.3

22.4

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II. THE CARBON DIOXIDE ABSORPTION CURVE AND CARBON DIOXIDE TENSION OF THE BLOOD IN CARDIAC DYSPNEA.

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INTRODUCTION.

In cardiac dyspnea the carbon dioxide tension of the alveolar air as determined by the Haldane method is lower than normal in comparison with the plasma bicarbonate as measured by means of the Van Slyke pipette (1, 2). The ratio between these two in health and in most pathological conditions has been shown by Van Slyke, Stillman, and Cullen (3), Walker and Frothingham (4), and Peters (1, 5) to be very close, varying from the mean by only 10 per cent. The existence of such a close relation might well be expected in the light of current theories with regard to the physicochemical control of the respiratory mechanism. That this relation should be disturbed in cardiac dyspnea is hardly extraordinary.

In the average normal person at rest carbon dioxide content, carbon dioxide tension, and hydrogen ion concentration of arterial and of venous blood all vary within comparatively narrow limits both individually and in relation to one another. Furthermore, the physicochemical regulatory mechanism is so delicately adjusted that changes in any of these factors are reflected in an immediate response on the part of the respiratory mechanism, which produces a compensatory alteration of the alveolar CO_2. As long as the sensibility of the respiratory center and the mechanical facilities for the exchange of gases between the blood and the air in the lungs remain unaffected, changes in any of these factors are instantly compensated by changes in one or all of the others. If either the

sensibility of the respiratory center or the mechanical facilities for the elimination of CO_2 in the lungs are impaired, one or all of the normal interrelations must be disturbed.

In cardiac decompensation, with dyspnea, there is evidence that the efficiency of the lungs as a means for the oxygenation of the blood and the elimination of CO_2 is greatly reduced (2, 6). There is also a possibility that the circulation is retarded.

In an attempt to throw some light on the exact cause of the discrepancy between alveolar and plasma values we first devoted our attention to a study of those factors of the respiratory system that may be termed mechanical: the function of the lungs and the upper respiratory tract. The results of this study have been published. It was found that air obtained by the Haldane method from patients with cardiac dyspnea was comparable in a functional sense to that obtained from trained normal subjects (2). That is, the air so obtained was the air employed for the exchange of gases between the blood and the outside air and was the only air available for this purpose. Realizing the objections that might be raised to the use of the term "alveolar" air in this sense, we suggested the terms "effective" or "exchange" air. By this means we evaded the criticisms which had been advanced by Siebeck (6). The latter, in the course of some studies of the lung volume in cardiac decompensation, came to the conclusion that the lungs in this condition failed to function efficiently as a tonometer. He decided that the mixing of gases in the lungs was imperfect and that methods for obtaining alveolar air were inapplicable. However, he considered the alveolar air only as a means of ascertaining the carbon dioxide tension of the arterial blood. Although our findings were not entirely in accord with Siebeck's, no attempt to controvert his statement was made. The question of the relation of alveolar CO_2 to arterial tension was entirely ignored, although its importance was fully recognized. Further studies convinced us that the effective lung volume was diminished (7) and the effective ventilation increased (8) in cardiac decompensation. Pearce (9) had proposed as an explanation of the disturbance of the alveolar: plasma ratio a retarded circulation. In view of the changes in the lung volume and the findings of Siebeck, however, this could not be definitely proved by the ordinary respiratory methods. Pearce assumed what Siebeck denied,

the applicability of alveolar methods as a means of determining arterial CO_2 tension. Even in normal subjects such an assumption seemed to be open to some criticism. The only direct evidence of a definite relation between alveolar and arterial CO_2 tension was given by Krogh and Krogh (10) in some tonometric experiments on animals. There was no evidence of any kind that a similar relation existed in diseases involving disturbances of the respiratory mechanism. Obviously it was necessary to find a means to measure the arterial CO_2 tension and to compare this with the alveolar CO_2 tension. For this reason the method described in the first paper was employed in the study of patients with cardiac decompensation. The CO_2 absorption curves of seven patients were obtained one or more times. Complete experiments were made on four cases out of seven. The results of these experiments are collected in Table III, arranged as were those of the normal subjects in Table VI of Paper I. Detailed protocols of all seven cases are presented at the end of this paper.

Level of the Absorption Curve in Cardiac Dyspnea.

The absorption curves of normal individuals fall within certain definite limits and are constant and characteristic for any given individual. This is far from the case in pathological subjects. The variations in both group and individual are considerable. The limits of normal variations in height are about 43 to 56 volumes per cent. The limits of variation of twenty-two patients with various pathological conditions were 32.4 to 70.2 volumes per cent, about three times as great. It is probable that a study of more patients with a greater variety of pathological conditions would show a still greater range of variation. In relatively few cases has more than one observation been made; but in these few the changes in height at different times are also quite striking. The maximum change observed was in Case 11, whose curve rose from 36.2 to 51.1 in the course of 4 days. Such fluctuations are not restricted to conditions of recognized acidosis, such as is found in diabetes mellitus or in nephritis. They occur also in cardiac valvular disease and in severe anemia.

The height of the absorption curves of seven decompensated cardiac patients, on whom eleven observations were made, varied from 32.4 to 52.0 volumes per cent, with an average value of 44.7

TABLE I.

Absorption Curve at 40 Mm. CO_2 Tension in Seven Patients with Cardiac Decompensation and Dyspnea.

Case.	Diagnosis.	CO_2 content.
		vol. per cent
6. G. B.	Paroxysmal tachycardia. Some dyspnea; considerable cyanosis; fluid in right pleural cavity and in abdomen; edema of both ankles; temperature 103°	45.4
7. J. D. B.	Aortic regurgitation. Mar. 19. Able to be up and about ward, but showed moderate dyspnea and orthopnea, with faint cyanosis of lips and finger-tips even while at rest	45.0
	Apr. 30. Condition practically unchanged	47.5
8. E. H.	Mitral stenosis; auricular fibrillation. Marked dyspnea and orthopnea; considerable cyanosis; general edema; hydrothorax and ascites	47.5
11. J. K.	Mitral stenosis; auricular fibrillation.	
	Apr. 16. Extreme cyanosis; moderate hyperpnea and edema	36.2
	Apr. 20. Cyanosis and hyperpnea improved	51.1
10. J. M.	Mitral stenosis; auricular fibrillation.	
	Apr. 9. Extreme cyanosis; moderate dyspnea and edema	38.7
	Apr. 23. Cyanosis continues; dyspnea and edema gone; still some hyperpnea	48.1
9. P. O. S.	Aortic regurgitation.	
	Mar. 9. Marked dyspnea with irregular breathing. Moderate cyanosis; considerable edema with hydrothorax	52.0
	Mar. 23. Symptoms steadily increasing	48.1
12. C. C.	Mitral stenosis. Marked cyanosis; moderate hyperpnea	32.4
Maximum		52.0
Minimum		32.4
Average		44.7

volumes per cent (see Table I and Fig. A). Of the seven patients three showed a definite reduction of the alkali reserve of the blood during the stage of most severe decompensation. Later observations on two of these, at the time when compensation was becoming reestablished, gave normal values. The other four cases showed no departure from the normal as regards the height of their curves.

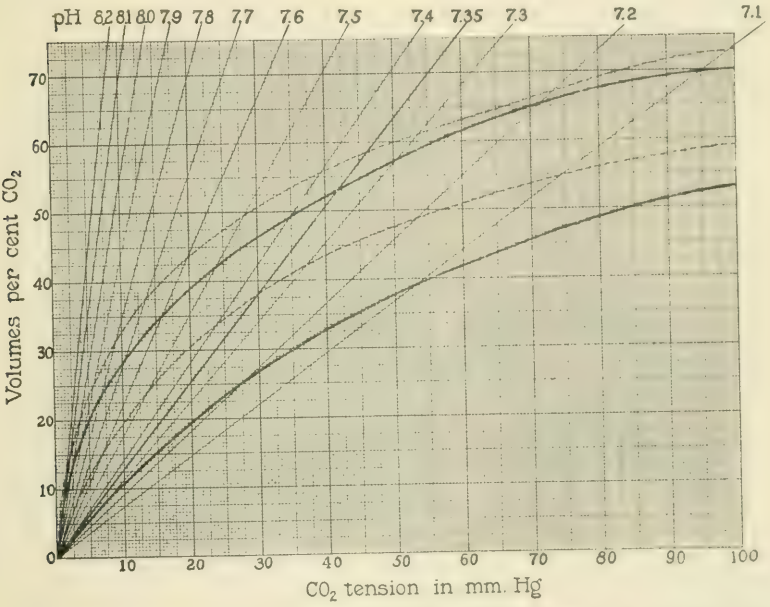

FIG. A. A comparison of limits of absorption curves of normal and cardiac subjects.

Limits of cardiac curves.

Limits of normal curves.

A low absorption curve is not a characteristic of the condition of cardiac decompensation. What factors determine the presence of such a curve in certain cases is not clear. As we shall show later, there is a relative retention of carbon dioxide in the arterial and venous blood of the cases with acidosis. This, in itself, should tend to produce an increase rather than a reduction of the alkali reserve, according to Henderson and Haggard (11).

It has been demonstrated by several observers, using various methods, that reduction of the partial pressure of oxygen in the blood produces a reduction of carbon dioxide tension and carbon dioxide content of the blood (12–15). However, in these studies the reduction of oxygen tension was produced in such a way that CO_2 was not allowed to accumulate in the blood. Whether a similar reduction in the level of the absorption curve will be produced by low oxygen in the presence of CO_2 accumulation has not been determined. That there is a certain amount of oxygen

TABLE II.

Comparison of CO_2 Capacity of Whole Blood and Oxygen Unsaturation of Blood.

Subject and diagnosis.	Date.	CO_2 capacity of blood.	Oxygen capacity of blood.	Oxygen content.		Oxygen saturation.	
				Arterial blood.	Venous blood.	Arterial blood.	Venous blood.
	1920	*vol. per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*	*per cent*	*per cent*
1. J. P. Normal.....	Mar. 12	55.9	22.5	19.8		88.0	
2. D. P. B. "	May 14	43.6	21.4	19.3	6.9	90.2	32.2
3. W. S. M. "	" 21	48.2	24.9	21.9	5.8	88.0	23.3
4. M. C. Asthma and emphysema.....	" 12	49.0	21.3	17.2	11.0	80.8	51.7
5. H. R. Polycythemia.	Apr. 28	47.9	23.9	22.6	9.0	94.6	37.7
6. J. K. Cardiac.....	" 20	51.1	26.5	25.0	22.5	94.3	84.9
7. J. M. "	" 23	48.1	20.8	22.0	11.0	100.0	52.9
8. J. D. B. "	" 30	47.5	13.9	14.3	3.7	100.0	26.6
9. G. B. "	Mar. 24	45.4	21.7		5.0		23.0
10. J. M. "	Apr. 9	38.7	20.2	16.7	8.5	82.7	42.1
11. J. K. "	Mar. 16	36.2	26.5	24.2	9.9	91.3	37.4
12. C. C. "	Apr. 9	32.4	18.3	18.0	3.2	98.4	17.5

unsaturation in the arterial blood and a very marked degree of oxygen unsaturation in the venous blood of some patients with cardiac decompensation has been shown by Harrop (16). As the most notable feature of the three patients with low absorption curves was a degree of cyanosis out of all proportion to the degree of dyspnea and hyperpnea, it seemed possible that the height of the absorption curve might bear some relation to the degree of oxygen unsaturation of the arterial and the venous blood.

That no such relation can be clearly established in our cases is evident from Table II, in which are shown the height of the carbon

dioxide absorption curve, and the oxygen content and saturation of both arterial and venous blood. At least, if the low curve is due to oxygen unsaturation, this is not the only active factor.

Although the restoration of compensation was associated with a return of the absorption curve to its normal level in Cases 10 and 11, the height of the absorption curve is no indication of the severity of the cardiac decompensation. The three cases with low curves were discharged from the hospital improved, while Cases 6, 8, and 9 with normal curves, failed to improve and died shortly after the observations reported.

There was nothing in the clinical picture to suggest a nephritic acidosis in any of these cases as the cause of the low absorption curves. Rather complete renal functional studies were made in Case 10. His blood non-protein nitrogen was only 43 mg. per 100 cc. and his phenolsulfonephthalein excretion 60 per cent in 2 hours.

We are then left to the conclusion that cardiac decompensation is sometimes associated with a real reduction of the alkali reserve of the blood, which disappears when compensation is reestablished. Why this should occur in some instances and not in others is not explained.

Arterial and Venous Carbon Dioxide Tension and Hydrogen Ion Concentration and Alveolar Carbon Dioxide Tension in Cardiac Dyspnea.

Complete experiments were made on four out of the seven cases with cardiac decompensation. The results of these experiments appear in Table III (arranged as were those of the normal subjects in Table VI, Paper I), and in Charts 7, 10, 11, and 12 inclusive. If the general averages in Table III are compared with those in Table VI, Paper I, the following points of distinction appear:

1. Although there is little difference in the range of variation of arterial CO_2 tension in the two tables, the CO_2 tension during cardiac dyspnea is high in relation to the level of the absorption curve because the absorption curves are low in three of the four subjects.

2. The consequence is that the arterial pH values in cardiac dyspnea are on the average lower than normal, indicating a carbon dioxide retention in the arterial blood.

TABLE III.

Results of the Study of Seven Cardiac Patients with Dyspnea.

Subject.	Date.	Alveolar CO_2 tension.	Alveolar reaction.	Arterial CO_2 content.	Arterial CO_2 tension.		Arterial reaction.		Venous CO_2 content.	Venous CO_2 tension.		Venous reaction.		Difference between arterial and alveolar CO_2 tension.	Difference between venous and arterial CO_2 content.	Difference between venous and arterial CO_2 tension.	Difference between venous and arterial reaction.
					Uncorrected.	Corrected.	Uncorrected.	Corrected.		Uncorrected.	Corrected.	Uncorrected.	Corrected.				
		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
	1920	*mm. Hg*	*pH*	*vol. per cent*	*mm. Hg*	*mm. Hg*	*pH*	*pH*	*vol. per cent*	*mm. Hg*	*mm. Hg*	*pH*	*pH*	*mm. Hg*	*vol. per cent*	*mm. Hg*	*pH*
6. G. B.	Mar. 24								54.8	61.0	47.2	7.19	7.26				
7. J. D. B.	" 19	25.2	7.42						49.8	50.5		7.23					
	Apr. 30	27.6	7.42	49.1	42.5	42.5	7.30	7.30	52.7	53.0	46.5	7.25	7.30	14.9	3.6	4.0	0.00
8. E. H.	Mar. 10								51.1	46.5		7.29					
9. P. O. S.	" 9								62.1	61.0		7.25					
	" 23								56.9	65.5		7.18					
10. J. M.	Apr. 9	26.0	7.34	39.6	40.5	38.0	7.23	7.25	49.8	61.0	52.3	7.15	7.22	13.0	10.2	14.3	0.03
	" 23	33.0	7.37	54.0	52.2	52.2	7.26	7.26	63.4	75.0	65.2	7.16	7.23	19.2	9.4	13.0	0.03
11. J. K.	" 16	22.0	7.32	35.9	39.7	38.0	7.20	7.20	45.5	62.3	47.5	7.10	7.21	16.0	9.6	9.5	−0.01
	" 20*	(32.5)	(7.41)	(52.4)	(42.25)	(41.25)	(7.34)	(7.35)						(8.75)			
12. C. C.		27.4	7.22	33.5	42.5	42.5	7.13	7.13	42.9	62.5	50.0	7.06	7.17	15.1	9.4	7.5	−0.04
Maximum*.....		33.0	7.42	54.0	52.2	52.2	7.30	7.30	63.4	75.0	65.2	7.29	7.30	19.2	10.2	14.3	0.03
Minimum*.....		22.0	7.22	33.5	39.7	38.0	7.13	7.13	42.9	46.5	46.5	7.06	7.17	13.0	3.6	4.0	−0.04

* The values obtained from the experiment of Apr. 20 on J. K. have been omitted in the summary of maximum and minimum values because on this date J. K. had recovered from his cardiac decompensation.

3. The alveolar CO_2 tension is, as has been previously pointed out, lower than normal. It is variable in relation to the absorption curve and may be, as in Case 12 (Chart 12), comparatively high, giving an alveolar pH far below the normal limits.

4. The difference between alveolar and arterial CO_2 tension is consistently increased. In five experiments on dyspneic cardiac patients this difference never fell below 13 mm. and in one case it reached the astonishing figure of 19 mm.

5. The venous CO_2 tension falls within normal limits, but, like the arterial, is high in relation to the level of the absorption curve.

6. There is no consistent increase in the difference between arterial and venous CO_2 content or tension, although in one or two instances both were slightly above the normal limits.

When each of these factors is studied in relation to the individual subjects of these experiments, it is apparent that only one is definitely and consistently present in every instance of cardiac dyspnea: this is the increase in the difference between alveolar and arterial CO_2 tension.

Although the average arterial CO_2 tension is relatively high and the arterial pH, in consequence, lower than normal, in Cases 7 (Chart 7) and 10 (Chart 10) the pH of the arterial blood is quite within normal limits. Can one say, then, that a carbon dioxide retention is characteristic of cardiac dyspnea, or does it occur only in certain cases, possibly those who show a considerable reduction in the height of the absorption curve, as do Cases 11 and 12? Unfortunately the range of variation in the normal arterial pH makes this question hard to answer. Absolute values are of little assistance in judging relative factors. Our results suggest that different normal subjects maintain the pH of their arterial blood at different levels. Furthermore the resting arterial pH level seems to be characteristic and constant for a given individual, as is the level of the absorption curve itself. In this case an arterial pH which is normal for one individual might mean a considerable retention of carbon dioxide in the case of another.

The statement was made above that there was nothing characteristic about the height of the absorption curve of the blood of patients with cardiac dyspnea, but that in certain cases low curves were found, indicating a diminution of the available alkali of the blood. We were then considering the absolute level of the

absorption curve. Again attention must be called to the fact that we are dealing in relative values only and that absolute levels, although satisfactory for purposes of clinical study, give little information with regard to functional changes in physiology or pathology. In order to ascertain whether a given pathological condition has changed the level of either the absorption curve or the arterial pH of an individual, it is not enough to know the limits of variation of normal individuals as a group. It is necessary to know the normal resting absorption curve and arterial pH of the given subject under investigation. In clinical investigations this is not always possible. Patients with severe cardiac dyspnea do not invariably recover. Of our seven cases three died without any intervals of improvement (Cases 6, 8, and 9); one (Case 7) had a chronic cardiac decompensation which resisted treatment, increasing gradually but steadily. Cases 10 and 11 improved. The former never completely recovered compensation; the latter made a very rapid recovery and was discharged without dyspnea or hyperpnea. Two determinations of the absorption curve were made on the blood of four of the seven patients: Cases 7, 9, 10, and 11.

In Case 9 the second observation, made 2 weeks after the first, revealed a drop of 4 volumes per cent in the height of the absorption curve. During this time the condition of the patient had continuously grown worse. The two observations on Case 7, at an interval of almost 6 weeks, were only about 2 volumes per cent apart. The second was the higher. There was little change in Case 7's condition on these two occasions. Possibly his dyspnea was a little more severe in the earlier experiment; his general condition seemed a trifle less favorable at the time of the second observation. The changes in absorption curve and in condition are, in any event, of no significance.

The rise in level of the absorption curves that occurred during the clinical improvement of Cases 10 and 11 is very striking. Although it is impossible, then, to say that cardiac dyspnea is always attended by a lowering of the absorption curve, there is a suggestion that such an association is not uncommon.

For the arterial pH our data are much more meager. This was determined in only four cases and in only two of these were two determinations obtained. In one of these, Case 10, the pH

remained unchanged in spite of a rise in the level of the absorption curve; in the other, Case 11, both pH and absorption curve rose. The latter regained compensation more completely than did the former in the interval between observations. The second experiment on Case 11 gives normal results in all essentials. Even the difference between alveolar and arterial CO_2 tension has returned to normal limits. It is quite conceivable that the picture presented by Case 10 on April 23 represents a preliminary step on the way to compensation and that, with complete recovery, which never occurred, the arterial pH would also have risen. There is no doubt that Case 12 had an uncompensated acidosis because his arterial pH lay below the normal limits. A definite carbon dioxide retention or uncompensated acidosis[1] occurred in two subjects, then. In the others a similar condition cannot be excluded as the result of our experiments although the arterial pH lay within normal limits.

There is nothing questionable about the increased difference between arterial and alveolar CO_2 tension. It occurred consistently in the presence of dyspnea and returned to normal in the one instance in which compensation was definitely reestablished. It is inconceivable that such a difference is due merely to errors in analytical methods or in calculation. It has been shown that the assumption that the alveolar air is in carbon dioxide equilibrium with the arterial blood is not always in keeping with the facts. That such differences as occurred in normal resting subjects might be only temporary was pointed out. But in cardiac dyspnea the differences are far greater and are invariably present.

Such a difference in itself might be produced by a diminution of the rate of the circulation. The venous blood might return to the lungs with an accumulation of carbon dioxide too great to permit complete removal in the lungs. The CO_2 remaining would pass on into the arteries and produce an increase in ventilation by its action on the respiratory center. In this case the difference between arterial and venous CO_2 tension and arterial and venous CO_2 content should be increased. Such an increase

[1] By a carbon dioxide retention or uncompensated acidosis we mean an accumulation of carbon dioxide sufficient to produce a real change in the pH of the blood.

is sometimes found, but it is not consistent and bears no relation to the arterial-alveolar discrepancy. The differences between arterial and venous CO_2 tension and arterial and venous CO_2 content in Case 7, for instance, are only 4.0 mm. and 3.6 volumes per cent respectively, while the arterial-alveolar difference is 14.9 mm. In addition to our own experiments we have calculated the differences between arterial and venous CO_2 content and CO_2 tension in ten of Harrop's (16) cardiac cases who showed definite evidences of decompensation. The calculations were made by the same formula employed in the normal cases (see Paper I). The results appear in Table IV and can be compared with Harrop's normal cases in Table VIII, Paper I. In his cases, as in ours, there is little evidence of a diminished circulation rate. A retarded circulation would seem to be, therefore, at the most only an occasional minor cause of the difference between arterial and alveolar CO_2 tension.

The predominant cause must lie in the lungs themselves. There must be an interference with the escape of CO_2 from the blood in the pulmonary circulation. This seems the more probable because of the known changes in the effective lung volume (7, 17). There may be portions of the lungs in which the circulation is more or less intact, but which contain no air. Or there may be portions of the lungs which are air-containing, but immobile and not adequately ventilated by the respirations. The latter is the view of Siebeck (6). Present methods of measuring lung volume have failed to settle the question because they are capable of measuring only the portions of the lungs that contain air available for respiratory purposes. Whether or not there is a true carbon dioxide retention in all cases of cardiac dyspnea, there is always an interference with the elimination of CO_2 from the blood and, therefore, a compensated or potential acidosis.

If the alveolar air is considered from the standpoint of respiratory mechanics, as a measure of the effective ventilation, a greater effective ventilation is necessary in order to maintain a given arterial carbon dioxide tension in the case of the patient with cardiac dyspnea than is necessary in the case of the normal person. To what extent does this account for the increase in the hydrogen ion concentration of the arterial blood? Does the alveolar carbon dioxide tension always indicate a ventilation in

excess of the normal in relation to the height of the absorption curve? If this were true the alveolar pH should always be considerably above 7.30. This is not true in Case 10, April 9, Case 11, April 16, and Case 12. In these instances the alveolar carbon dioxide is at or below the normal limit in relation to the height of

TABLE IV.

Difference between Arterial and Venous CO_2 Tension.

(Calculated from observations on patients with cardiac decompensation, presented by Harrop.)

Case No.	Arterial CO_2 content.	Arterial oxygen content.	Venous CO_2 content.	Venous oxygen content.	Difference between arterial and venous CO_2 content.	Difference between arterial and venous CO_2 tension.	Oxygen capacity.
	vol. per cent	*vol. per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*	*mm. Hg*	*vol. per cent*
1	46.4	17.2	54.0	6.9	7.6	15.4	20.3
	46.3	19.6	48.7	16.3	2.4	4.9	21.8
	44.3	22.3	56.1	15.5	11.8	27.2	23.1
2	45.4	17.1	48.3	9.3	2.9	4.6	19.0
	48.2	17.9	52.7	9.5	4.5	8.4	18.7
	49.6	17.8	53.1	12.6	3.5	6.9	18.5
4	41.4	13.9	44.2	10.8	2.8	5.9	16.8
	43.5	15.2	46.5	9.6	3.0	5.6	16.6
5	38.9	17.7	41.8	6.3	2.9	3.3	19.9
	42.7	18.2	47.1	10.4	4.4	8.3	19.7
	43.8	17.9	47.6	13.1	3.8	7.8	19.6
7	38.7	16.5	43.2	7.3	4.5	7.5	18.9
	42.9	20.5	46.5	16.1	3.6	7.5	22.9
	43.6	21.1	49.0	15.4	5.4	5.5	22.5
8	31.4	19.3	37.5	11.1	6.1	12.4	20.7
	42.8	21.3	45.7	11.6	2.9	3.9	22.5
	41.5	22.5	46.5	17.6	5.0	10.8	23.3
Maximum..	49.6		56.1		11.8	27.2	
Minimum..	31.4		37.5		2.4	3.3	
Average....	43.0		47.6		4.5	8.6	

the corresponding absorption curves. Although these three patients showed some dyspnea the ventilation was insufficient to compensate for the low absorption curves they presented. Nor was this due to the fact that they had passed the limits of compensation and were unable to increase their ventilation

further. In none of these cases was dyspnea a prominent feature. The actual minute volume of respiration of Case 10 was only 8,650 cc. with a respiratory rate of 18 per minute. This suggests that the uncompensated acidosis found in these cases was not due entirely to an inability of the injured respiratory mechanism to effect the proper carbon dioxide elimination, but to the fact that the respiratory center was not so sensitive as normal to its natural stimulus, the hydrogen ion concentration of the blood. As the comparative lack of dyspnea shown by these patients is not at all typical of cardiac decompensation, this insensibility of the respiratory center to the natural acid stimulus is not necessarily a characteristic of cardiac dyspnea *per se*.

In the normal subjects the pH of the arterial and venous blood was found to be almost identical in spite of a considerable difference in CO_2 content. This was possible because of the effect of oxygen on the absorption curve. The same holds true of the cardiac cases, in some of whom even larger differences of CO_2 content occur. The difference in pH of arterial and venous blood never exceeds 0.04 and is, therefore, within the limits of error of the method.

One may pause for a moment to consider what bearing the presence of a carbon dioxide retention in association with a low absorption curve may have on the work of Henderson and Haggard (11). They claim that any damming back of carbon dioxide causes the blood to abstract alkali from the tissues and produces a rise in the level of the absorption curve. The facts here established for cardiac dyspnea are quite at variance with such a theory unless one argue from a teleological standpoint that the damming back of carbon dioxide is produced in an attempt to withdraw alkali from the tissues and thus restore the alkali of the blood to its normal level. Aside from the fact that this ascribes to the blood a purposeful effort at compensation, this is not the usual reaction to a reduction in the level of the absorption curve as is evidenced by the curves of nephritis patients (see Case 5, Paper I, and Case 16, Paper III).

It is interesting to compare the relations that obtain in cardiacs with those found by Means, Bock, and Woodwell (18) in pneumonia and with those found by us in one case of severe asthma and emphysema with extreme cyanosis (Case 13, Chart 13).

These investigators found a carbon dioxide acidosis in three pneumonia patients, without any reduction in the level of the absorption curve. They, however, accept Henderson's view that oxygen does not affect the absorption curve of blood. Fortunately they have published figures which allow us to make corrections by our formula. As we have calculated their results the arterial pH values in their three cases are: for E. D., 7.23 uncorrected, 7.28 corrected; for G. A., 7.30 uncorrected, 7.35 corrected; for N. D., 7.27 uncorrected, 7.30 corrected. Because of the degree of oxygen unsaturation in the arterial blood of pneumonia patients these corrections are much larger than the corresponding corrections in cardiac dyspnea, where the oxygen unsaturation of the arterial blood is usually comparatively slight. If oxygen does affect the CO_2-combining capacity of blood there is little evidence of a carbon dioxide acidosis in these figures alone.

Case 13 had an asthmatic condition of long standing with an extreme emphysema and the most extraordinary cyanosis. His face and extremities were at all times a deep purple and during his acute attacks were almost black. The experiment was performed during one of these attacks. His absorption curve lies at a normal level. His arterial tension is quite high in proportion and about 18 mm. higher than the alveolar tension, which lies at a pH of 7.33. The corrected arterial pH is 7.22. The most striking thing about his chart is the enormous venous carbon dioxide tension. Although the difference between the arterial and venous carbon dioxide content is only 5.7 volumes per cent, the portion of the absorption curve on which the arterial and venous points lie is so flat that this represents a change of CO_2 tension of about 40 mm. uncorrected, as far as we can tell by extrapolating the venous point. The compensating effect of oxygen is, however, also increased by the flatness of the curve sufficiently to reduce the venous tension about 35 mm. (In calculating the effect of oxygen on the venous point in this case we were unable to use our formula because the CO_2 tension was above 70 mm. A value for K of 0.414 was used instead of the usual 0.34. This is the average value of K between 70 and 90 mm. From Table I it appears that there is a considerable variation in the value of K above 70 mm. and there may be a large error in this correction.) In spite of this there is still a very

considerable difference in pH between the arterial and venous blood. This difference is, however, much less than would occur if the arterial tension were lower on a curve of the same level, because of the difference in the slope of the pH lines. In a study of these factors may lie an explanation of the relatively great tolerance for carbon dioxide found by Scott (19) in emphysema patients. No general conclusions can be drawn from this one patient as to the respiratory mechanism in emphysema or asthma. The picture is similar to that of cardiac dyspnea in the fact that there is a marked difference between the alveolar and the arterial CO_2 tension, suggesting again a functional impairment of the ventilating power of the lungs. Furthermore, there is a carbon dioxide retention, as evidenced by the low arterial pH.

Plasma Bicarbonate as a Measure of the Alkali Reserve.

As a result of a large series of observations of the carbon dioxide-combining capacity of the venous plasma of decompensated cardiac patients made in 1916 and subsequently, we were led to conclude that the alkali reserve of the blood of these patients, although quite variable, lay for the most part within normal limits. The same thing is true of the present cases, if we consider the carbon dioxide capacity of the plasma. Six determinations in this series vary from 55.0 to 75.7 volumes per cent. Among these is a determination made on Case 11 from the same specimen of blood that showed such a marked reduction in the height of the absorption curve.

The contradictory results obtained from whole blood and from venous plasma may be explained by variations in the carbon dioxide content of the venous blood. As the tension of carbon dioxide in blood is increased the bicarbonate of the blood also increases. This is evidenced by the fact that the slope of the absorption curve is greater than that of the curve which represents the solubility of carbon dioxide in the blood. The increase in the bicarbonate of blood in response to increases of CO_2 tension is associated with a transfer of base from cells to plasma. Joffe and Poulton (20) have demonstrated that the change in bicarbonate content of whole blood is reflected in the plasma. This had already been clearly demonstrated by Van Slyke and Cullen (21). Van Slyke and Cullen, Straub and Meier (22), and

others have shown that the CO_2 absorption curve of plasma is much flatter than that of whole blood, approaching more nearly the curve of a simple bicarbonate solution.

In this case the carbon dioxide-combining capacity of the venous plasma must be dependent, to some extent at least, upon the carbon dioxide tension or content of the venous blood at the time that it is withdrawn. Table V shows this relation clearly. In this table are represented the carbon dioxide content of venous blood, drawn directly, without stasis, beneath albolene; the

TABLE V.

Relation between CO_2 Content of Venous Blood and CO_2 Capacity of Venous Plasma.

Subject.	CO_2 capacity of whole blood.	CO_2 content of venous blood.	CO_2 capacity of venous plasma.
	vol. per cent	*vol. per cent*	*vol. per cent*
A. B.	60.8	63.9	69.1
J. M.	48.1	63.3	75.7
M. C.	49.0	63.2	74.5
P. O. S.	52.0	62.1	74.2
J. P.	55.9	62.0	73.0
H. R.	47.7	60.2	68.6
N. B.	52.7	60.1	66.0
D. P. B.	47.0	57.5	66.0
D. A.	42.1	57.2	68.0
D. P. B.	43.3	53.3	62.9
E. H.	47.5	51.1	64.0
J. D. B.	45.0	49.8	60.7
J. M.	38.7	49.8	59.4
E. S.	47.8	46.8	49.1
J. K.	36.2	45.5	55.0
H. G.	45.4	43.3	53.3

carbon dioxide capacity of whole blood at 40 mm. of CO_2 tension and 37.5°C.; and the carbon dioxide capacity of venous plasma determined according to the technique of Van Slyke (23). (For the last, venous blood was withdrawn under albolene, centrifuged in this condition, and the plasma removed to a separatory funnel and saturated with alveolar CO_2.) The observations are arranged according to the magnitude of the CO_2 content. The plasma capacity parallels the CO_2 content rather more closely than it does the CO_2 capacity of whole blood. But, if the CO_2 capacity

of the plasma is to be used as a measure of the bicarbonate content of the blood, it should vary directly as the CO_2 capacity of the whole blood.

The cardiac cases are not the only ones in which the plasma method fails to agree with the whole blood method. H. G. shows a slight acidosis on the basis of his plasma figures, although the whole blood CO_2 capacity is normal. In this case the venous carbon dioxide content is very low. The discrepancy is slight, but is quite striking in comparison with J. D. B., a cardiac patient with an absorption curve at the same level as that of H. G. Even in normal subjects estimations of the bicarbonates of whole blood from those of plasma may prove inaccurate. This is well illustrated in the case of D. P. B., who on several occasions showed a CO_2 capacity relatively higher in the plasma than in the whole blood.

In severe anemia the use of plasma may lead to misinterpretations. In this condition, as we shall show, the whole blood curve becomes relatively flat, approaching that of plasma. Changes in CO_2 tension, therefore, produce relatively small alterations in CO_2 content. The consequence is that the values obtained from whole blood are high in comparison with those obtained from plasma. This is especially noticeable in Cases A. B. and E. S. (The corresponding hemoglobin values were 32 and 35 per cent respectively.) This may explain the fact that Kahn and Barsky (24), studying the plasma in pernicious anemia, found a reduction of the alkali reserve in three cases, while the four cases in our series gave consistently high values for the CO_2-combining capacity of whole blood.

Finally, a further source of error lies in the fact that the absorption curves of plasma from different specimens of blood may differ. This has been demonstrated by Straub and Meier (22).

The use of the CO_2-combining power of the plasma as a measure of the alkali reserve will cause little or no error in most cases if it is employed only in those conditions in which the respiratory and circulatory systems are undisturbed and react in the normal manner to the natural stimuli. It was to subjects of this type that Van Slyke and coworkers (25) first applied it with such success that his method has become the standard method for the measurement of the alkali reserve. Henderson and Haggard

(26) have contended that whole blood is preferable to plasma. The latter, however, was chosen by Van Slyke with full recognition of the error involved, because of technical reasons, especially the fact that whole blood demanded immediate analysis, whereas plasma could be kept for a considerable length of time without deterioration. Furthermore, the coagulum produced by the addition of acid to whole blood rendered the cleansing of his pipette difficult. With the substitution of tartaric acid for sulfuric in the Van Slyke method one of the technical reasons for preferring plasma has been removed. The impossibility of keeping whole blood for any length of time remains an objectionable feature.

If, for this reason, the use of plasma is found necessary, variations in carbon dioxide saturation, the chief cause of error in the use of plasma, must be avoided. This can easily be effected by bringing the whole blood into equilibrium with a standard air-CO_2 mixture, *e.g.* alveolar air, before removing the plasma. If this were done at least the chief objection to the use of plasma would be removed. However, the air-CO_2 mixture used for saturation of whole blood must be more carefully standardized than is the case when plasma is employed. This is evident from the differences in the absorption curves of whole blood and plasma. Small variations in carbon dioxide tension have a much greater effect on the carbon dioxide content of whole blood. The use of alveolar air, which is the usual procedure with plasma might, with whole blood, introduce a perceptible error. Under resting conditions the alveolar CO_2 tensions of normal individuals should not vary by more than a few millimeters. As the corresponding change in the carbon dioxide content of the blood is only half as great, the use of alveolar air by an operator trained in respiratory methods should produce no serious errors.

Under these conditions plasma should give values that are dependable as far as the ability of the blood to neutralize acids other than carbonic is concerned. For the study of the respiratory function of the blood, on the other hand, whole blood alone can be used. In order to avoid unnecessary complications, the normal limits of variation at room temperatures will have to be more definitely established, as whole blood work up to the present has been confined almost entirely to physiological studies and saturation has been effected at body temperature.

Just as this paper was approaching completion the final report of the work of Joffe and Poulton (20) on the absorption curves of whole blood and plasma appeared. On the basis of their findings they also conclude that the carbon dioxide capacity of plasma separated from venous blood is not a proper measure of the available alkali of the blood. They advise a method identical with that here proposed.

Up to the time that Van Slyke published his method the presence of a carbon dioxide retention had not yet been demonstrated in any pathological condition, and, although the possibility of such an occurrence was clearly recognized by him, it did not seem of sufficient practical importance to outweigh the obvious technical advantages of plasma over whole blood. As applied to the study of diabetes the use of plasma probably introduced no serious error. When we presented our data to Dr. Van Slyke we found that he had come to practically the same conclusion as a result of some studies on anesthesia.

Carbon Dioxide Content of the Venous Blood in Cardiac Dyspnea.

It is clear that a discrepancy between the CO_2 capacity of whole blood and that of venous plasma may be produced by at least three factors: (1) An abnormal venous carbon dioxide tension; (2) a disturbance of the normal proportion of cells to plasma; (3) an abnormality in the carbon dioxide absorption curve of the plasma itself. The second of these we may assume to be unimportant in cardiac dyspnea, although we have not investigated the matter carefully. In the majority of cases hemoglobin determinations were made by means of the oxygen capacity and revealed no striking changes. The plasma absorption curve has not been determined. We have, however, studied the venous carbon dioxide content of a number of subjects.

The determination of the presence or absence of carbon dioxide retention in the venous blood is not so simple a matter as it may appear. The results obtained by previous observers are not at all consistent. Harrop (16) found that the difference between arterial and venous carbon dioxide content was sometimes increased in cardiac dyspnea, indicating a relative retention of carbon dioxide in the venous blood. Table IV gives a summary of Harrop's findings. The results obtained from the five cases

in our series appear in Table III. The two sets of observations are in essential agreement. The difference between arterial and venous blood was much more variable in decompensated cardiac cases than in normal subjects, and in some of the former was relatively increased. Scott (27) has recently reported the CO_2 content of the plasma of both arterial and venous blood lower than normal in cardiac decompensation. A few unpublished determinations made by one of us on venous plasma in 1916 were not in agreement with his findings. The values obtained were more variable than those obtained from normal subjects, but the variations were not predominantly low. In some cases they were quite high. The same is true of the values obtained from whole blood. Their only characteristic is a great range of variation (see Tables I and III). By comparison with Table V it will be seen that these variations bear a rough relation to the height of the absorption curves.

Neither Harrop's nor Scott's method can throw much light on the question of the presence or absence of a carbon dioxide retention. The absolute value for carbon dioxide content of either whole blood or plasma, whether arterial or venous, although of interest, cannot be accepted as a satisfactory criterion. The CO_2 content which is normal for a blood with a high absorption curve is excessive for a blood with a low absorption curve, if the reaction of the blood is to be maintained constant. The locus of points of equal pH is represented by straight lines passing through the origin. As the curves become lower, therefore, equal amounts of CO_2 have a greater effect in changing the pH. The presence of a carbon dioxide retention can only be determined, then, by a comparison of the carbon dioxide content of the blood with the height of the absorption curve. Such a comparison appears in the venous pH values in Table III. In the case of the three cardiac patients with low absorption curves (Cases 10, 11, and 12) there is a definite carbon dioxide retention which explains the falsely high values for bicarbonate obtained by the plasma CO_2 capacity method of Van Slyke (23).

SUMMARY AND CONCLUSIONS.

1. A study has been made of the carbon dioxide absorption curve of the blood of seven patients with cardiac decompensation

and dyspnea. In three out of the seven low curves were found. In two of these cases the curves returned to the normal level when compensation was reestablished. Clinically these patients were distinguished by the presence of an extreme degree of cyanosis with little dyspnea. No relation could be established between the reduction of the absorption curve and the oxygen unsaturation of the arterial or venous blood. A low absorption curve was not an indication of the severity of the condition. No signs of renal involvement were discovered in any of these cases.

2. The reduction of the alkali reserve indicated by these low absorption curves was not reflected in the plasma. The CO_2 capacity of the venous plasma is determined by the carbon dioxide tension at which it existed in the body rather than by the carbon dioxide-combining capacity of the blood. For this reason the determination of the plasma bicarbonates by the technique originally proposed is not applicable as a measure of the alkali reserve in conditions associated with CO_2 accumulation in the venous blood. A true measure of the bicarbonate content of blood is obtained from the carbon dioxide capacity of whole blood. As whole blood deteriorates when kept, while plasma does not, it may still be necessary to employ plasma for purposes of routine procedure. In this case errors due to variations in carbon dioxide saturation may be avoided by saturating the whole blood with a standard air-CO_2 mixture before separating the plasma. With this modification the method may be rendered applicable to the determination of the alkali reserve of the blood. For the study of the respiratory function of the blood, however, only whole blood should be used.

3. (*a*) In four cases arterial and venous carbon dioxide tension were determined. The alveolar carbon dioxide tension was also determined. The only consistent and characteristic finding was an increase in the difference between alveolar and arterial CO_2 tension. This difference varied from 13 to 19 mm.

(*b*) In two cases there was a definite CO_2 retention in the arterial and venous blood with a consequent lowering of the pH.

(*c*) No consistent increase in the difference between arterial and venous CO_2 content or tension could be demonstrated, although in one or two instances it was slightly greater than normal.

4. The causes of the discrepancy between the alveolar carbon dioxide tension and the carbon dioxide-combining capacity of the venous plasma in cardiac dyspnea are:

(*a*) The fact that the carbon dioxide capacity of the plasma gives values that are too high in the presence of carbon dioxide retention such as is sometimes found in cardiac dyspnea.

(*b*) The alveolar carbon dioxide is very low in proportion to the carbon dioxide content of the venous blood and does not bear a definite relation to the height of the absorption curve.

5. The causes of cardiac dyspnea seem to be: The fact that a greater ventilation is necessary to effect the normal carbon dioxide elimination. This is largely brought about by an impairment of the efficiency of the pulmonary mechanism for the exchange of gases between the blood and the outside air. This necessitates the maintenance of a greater difference in carbon dioxide pressure between the blood in the pulmonary circulation and the alveolar air in order to effect the normal carbon dioxide output. To maintain the carbon dioxide tension and the hydrogen ion concentration at the proper level the alveolar carbon dioxide tension must be abnormally low. In some cases a diminution of the circulation rate may be an additional factor in the production of a carbon dioxide acidosis. Finally in a certain proportion of the cases, at least, there is a real reduction of the available alkali of the blood. In at least two cases with a reduction of the available alkali of the blood were found indications of a comparative insensibility of the respiratory center to its natural physicochemical stimulus, the hydrogen ion concentration of the blood.

BIBLIOGRAPHY.

1. Peters, J. P., Jr., *Am. J. Physiol.*, 1917, xliii, 113.
2. Peters, J. P., Jr., and Barr, D. P., *Am. J. Physiol.*, 1920–21, liv, 307.
3. Van Slyke, D. D., Stillman, E., and Cullen, G. E., *J. Biol. Chem.*, 1917, xxx, 401.
4. Walker, I. C., and Frothingham, C., Jr., *Arch. Int. Med.*, 1916, xviii, 304.
5. Peters, J. P., Jr., *Am. J. Physiol.*, 1917, xliv, 84.
6. Siebeck, R., *Deutsch. Arch. klin. Med.*, 1912, cvii, 253.
7. Peters, J. P., Jr., and Barr, D. P., *Am. J. Physiol.*, 1920–21, liv, 335.
8. Barr, D. P., and Peters, J. P., Jr., *Am. J. Physiol.*, 1920–21, liv, 345.
9. Pearce, R. G., *J. Lab. and Clin. Med.*, 1916–17, ii, 867.
10. Krogh, A., and Krogh, M., *Skand. Arch. Physiol.*, 1909–10, xxiii, 179.
11. Henderson, Y., and Haggard, H. W., *J. Biol. Chem.*, 1919, xxxix, 163.

12. Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C., *Phil. Tr. Roy. Soc. London, Series B*, 1912, cciii, 271.
13. Barcroft, J., The respiratory function of the blood, Cambridge, 1914, 243–265.
14. Lutz, B. R., and Schneider, E. C., *Am. J. Physiol.*, 1919, l, 280.
15. Parsons, T. R., Parsons, W., and Barcroft, J., *J. Physiol.*, 1919–20, liii, p. cx.
16. Harrop, G. A., Jr., *J. Exp. Med.*, 1919, xxx, 241.
17. Peabody, F. W., *Arch. Int. Med.*, 1917, xx, 433, 443.
18. Means, J. H., Bock, A. V., and Woodwell, M. N., *J. Exp. Med.*, 1921, xxxiii, 201.
19. Scott, R. W., *Arch. Int. Med.*, 1920, xxvi, 544.
20. Joffe, J., and Poulton, E. P., *J. Physiol.*, 1920–21, liv, 129.
21. Van Slyke, D. D., and Cullen, G. E., *J. Biol. Chem.*, 1917, xxx, 289.
22. Straub, H., and Meier, K., *Biochem. Z.*, 1918, lxxxix, 156; *Deutsch. Arch. klin. Med.*, 1919, cxxix, 54.
23. Van Slyke, D. D., *J. Biol. Chem.*, 1917, xxx, 347.
24. Kahn, M., and Barsky, J., *Arch. Int. Med.*, 1919, xxiii, 334.
25. Stillman, E., Van Slyke, D. D., Cullen, G. E., and Fitz, R., *J. Biol. Chem.*, 1917, xxx, 405.
26. Henderson, Y., and Haggard, H. W., *J. Biol. Chem.*, 1918, xxxiii, 333.
27. Scott, R. W., *Proc. Soc. Exp. Biol. and Med.*, 1919–20, xvii, 19.

EXPLANATION OF CHARTS.

Chart 7.

Case 7. J. D. B. Syphilitic aortitis. Dilatation of ascending aorta. Aortic insufficiency. Male, age 50 years, single, pastry cook.

Looks chronically ill. Moderate dyspnea even while at rest, but able to walk around ward. Faint cyanosis of lips and finger-tips. Lungs clear.

Heart very much enlarged, with loud systolic and diastolic murmurs, maximum over the aortic area. X-ray revealed aneurysmal dilatation of the ascending aorta.

Wassermann ++++.

Patient improved but slightly and is still in the hospital at the time of publication.

Experiment 1. Mar. 19, 1920.

Alveolar CO_2 before venous puncture, *mm*			25.5
			25.0
" CO_2 after " " "			25.2
CO_2 absorption curve:			
CO_2 tension, *mm. Hg*	77.2	47.7	23.8
CO_2, *vol. per cent*	62.9	48.7	37.1
	59.7		36.5
CO_2 content of venous blood, *vol. per cent*			49.8
CO_2 capacity of venous plasma (41.7 mm. Hg) *vol. per cent*			60.7
O_2 capacity of blood, *vol. per cent*			16.4

Experiment 2. Apr. 30. Condition practically unchanged, although cyanosis may be slightly increased.

Alveolar CO_2 before arterial puncture, *mm*				27.3
				27.1
				27.7
" CO_2 after " " "				27.6
CO_2 absorption curve:				
CO_2 tension, *mm. Hg*	59.8	47.2	28.4	
CO_2, *vol. per cent*	55.6	52.9	39.8	
	56.1	50.7	40.3	
CO_2 content of arterial blood, *vol. per cent*				49.3
				48.9
CO_2 " " venous " " " "				52.0
				53.4
Difference between arterial and venous CO_2, *vol. per cent*				3.6
O_2 capacity of blood, *vol. per cent*				13.9
O_2 content of arterial blood, *vol. per cent*				14.3
O_2 " " venous " " " "				3.7
O_2 consumption, *vol. per cent*				10.6
O_2 saturation of arterial blood, *per cent*				100
O_2 " " venous " " "				27
Respiratory quotient of blood				0.34

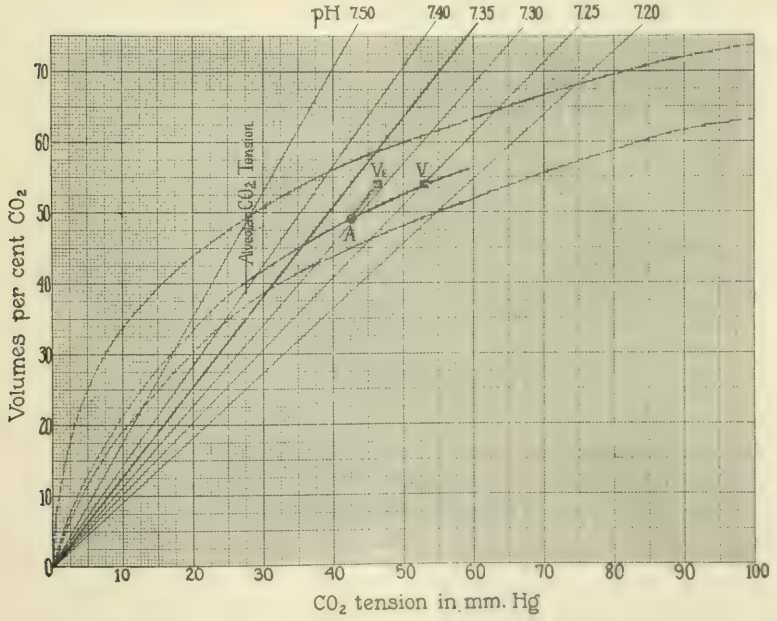

CHART 7. Experiment of Apr. 30. Directions for interpretation of charts are given in Paper I.

Chart 10.

Case 10. J. M. Mitral stenosis. Male, age 60 years, single, engineer. Looks chronically ill. Lies quietly in bed, without dyspnea or orthopnea. Very marked cyanosis of face and extremities. Veins of neck engorged, but not visibly pulsating. Brawny, pitting edema of feet and legs. Signs of moderate amount of fluid in the right pleural cavity. Liver very much enlarged and pulsating.

Temperature normal. Pulse absolutely irregular; rate 72 to 100. Blood pressure: systolic 138; diastolic 86. Heart moderately enlarged both to the right and left. Loud blowing, systolic murmur at apex, accompanied by rough thrill. No murmurs at base. Electrocardiogram shows auricular fibrillation.

Urine contains considerable albumin, with a few granular and hyaline casts. Specific gravity 1.023 to 1.027. Non-protein nitrogen of blood 43 mg. per 100 cc. Phenolsulfonephthalein excretion 60 per cent in 2 hrs. Discharged from hospital, improved, 1 week after last experiment.

Experiment 1. Apr. 8, 1920.

Minute volume of respirations, *cc*..... 8,652
Tidal air 475 cc. Respirations per min..... 18.2
CO_2 in expired air 2.40 per cent. CO_2 output per min., *cc.* 208
Vital capacity of the lungs, *cc*..... 1,197

Experiment 2. Apr. 9. Condition unchanged.

Alveolar CO_2 before arterial puncture, *mm*..... 25.0
CO_2 absorption curve:

CO_2 tension, *mm. Hg*.....	75.8	54.4	44.4
CO_2, *vol. per cent*.....	56.6	46.0	41.7

CO_2 content of arterial blood, *vol. per cent*..... 39.6
39.6
CO_2 " " venous " " " " 49.5
50.0
Difference between arterial and venous CO_2, *vol. per cent*... 10.2
CO_2 capacity of venous plasma (40.9 mm. Hg), *vol. per cent*.. 59.4
O_2 " " blood, *vol. per cent*..... 20.7
O_2 content of arterial blood, *vol. per cent*..... 16.7
O_2 " " venous " " " " 8.5
O_2 consumption, *vol. per cent*..... 8.2
O_2 saturation of arterial blood, *per cent*..... 83
O_2 " " venous " " " 42
Respiratory quotient of blood..... 1.24

Experiment 3. Apr. 23. Condition greatly improved. Quite comfortable. No edema. Signs of fluid in chest gone. Cyanosis still well marked. Heart action good, rate about 60, with practically no pulse deficit. Is able to be out of bed and to walk about ward without difficulty or discomfort.

Vital capacity of lungs, *cc*..... 2,463
Minute volume of respirations, *cc*..... 9,854
Tidal air 498 cc. Respirations per min..... 19.8

CO_2 in expired air 2.72 per cent. CO_2 output per min., *cc.* 268
Alveolar CO_2 before arterial puncture, *mm*..... 34.2
35.3
" CO_2 after " " " 31.2
CO_2 absorption curve:

CO_2 tension, *mm. Hg*.....	80.4	26.6
CO_2, *vol. per cent*.....	64.6	38.0
	63.9	40.5

CO_2 content of arterial blood, *vol. per cent*..... 53.8
54.2
CO_2 " " venous " " " " 63.0
63.7
Difference between arterial and venous CO_2, *vol. per cent*.. 9.3
CO_2 capacity of venous plasma (52.0 mm. Hg), *vol. per cent.* 75.7
O_2 " " blood, *vol. per cent*..... 20.8
O_2 content of arterial blood, *vol. per cent*..... 22.0
O_2 " " venous " " " " 11.1
11.0
O_2 consumption, *vol. per cent*..... 10.9 or 9.7
O_2 saturation of arterial blood, *per cent*..... 100
O_2 " " venous " " " 53
Respiratory quotient of blood..... 0.85 or 0.96

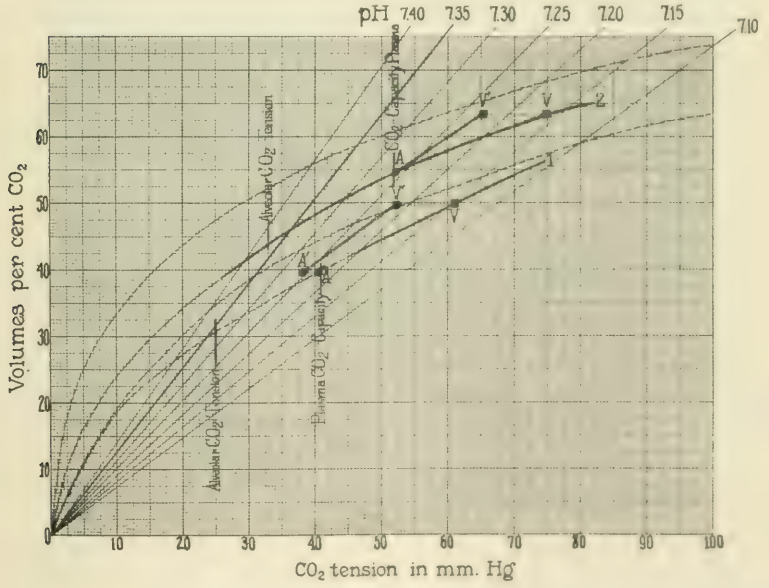

CHART 10. 1. Experiment of Apr. 9.
2. Experiment of Apr. 23.

CHART 11.

Case 11. J. K. Mitral stenosis. Male, age 35 years, single, elevator operator. Looks chronically ill. Lies quietly in bed with only slight dyspnea and orthopnea. Face and extremities are a livid purple. Slight, pitting edema of feet, ankles, and legs. Few sibilant and sonorous râles scattered throughout lungs, but no signs of pleural effusion. Liver enlarged and pulsating. Temperature normal. Pulse totally irregular, radial rate 55, heart rate 92. Blood pressure: systolic 140, diastolic 100. Heart enlarged both to left and right. Loud systolic and soft diastolic murmurs, maximum over apex. Pulmonic second sound accentuated. Electrocardiograms show auricular fibrillation.

Urine shows cloud of albumin, no casts. Specific gravity 1.018.

Discharged from hospital improved, 9 days after last experiment.

Experiment 1. Apr. 16, 1920.

Alveolar CO_2 before arterial puncture, *mm*			23.0
			22.1
" CO_2 after " " "			21.4
			21.4
CO_2 absorption curve:			
CO_2 tension, *mm. Hg*	68.0	47.1	36.7
CO_2, *vol. per cent*	47.7	38.3	35.8
	47.4	39.4	
CO_2 content of arterial blood, *vol. per cent*			36.8
			35.0
CO_2 " " venous " " " "			44.8
			46.1
Difference between arterial and venous CO_2, *vol. per cent*			9.6
CO_2 capacity of venous plasma (37.8 mm. Hg), *vol. per cent.*			55.0
O_2 " " blood, *vol. per cent*			26.3
			26.7
O_2 content of arterial blood, *vol. per cent*			24.2
O_2 " " venous " " " "			9.9
O_2 consumption of " " " "			14.3
O_2 saturation of arterial blood, *per cent*			91
O_2 " " venous " " "			37
Respiratory quotient of blood			0.67

Experiment 2. Apr. 20. Greatly improved. No dyspnea. Cyanosis less marked, but still considerable. Edema gone. Lungs clear. Pulse good quality. Heart rate about 40. No pulse deficit (digitalis heart block). Arthritis of left foot with temperature of 102°F.

Vital capacity of the lungs, *cc*	1,800
Alveolar CO_2 before arterial puncture, *mm*	30.2
	34.7
" CO_2 after " " "	32.5

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	37.8
CO_2, *vol. per cent*	49.1
	50.7
CO_2 content of arterial blood, *vol. per cent*	53.7
	51.0
O_2 " " " " " " "	25.0
O_2 " " venous " " " "	22.5
O_2 consumption, *vol. per cent*	2.5
O_2 saturation of arterial blood, *per cent*	94
O_2 " " venous " " "	85

(O_2 capacity of Apr. 16 used for calculations.)

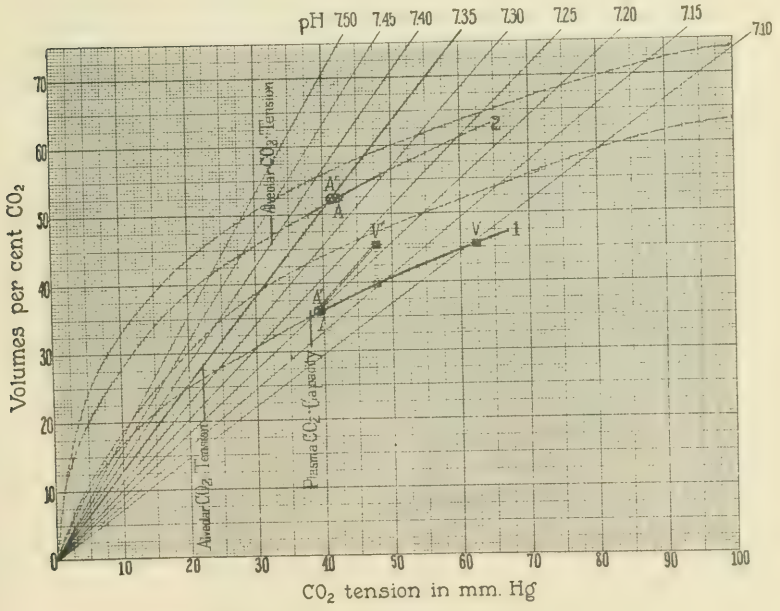

CHART 11. 1. Experiment of Apr. 16.
2. Experiment of Apr. 20.

Chart 12.

Case 12. C. C. Mitral stenosis. Looks chronically ill. Lies quietly in bed, with only slight dyspnea and no orthopnea. Very marked cyanosis of head and extremities. Somewhat irrational.

Experiment 1.

Alveolar CO_2 before arterial puncture, *mm*				28.0
				26.1
				27.8
" CO_2 after " " "				27.5
CO_2 absorption curve:				
CO_2 tension, *mm. Hg*	66.2	47.6	39.0	
CO_2, *vol. per cent*	43.7	34.8	33.0	
	45.3	35.9	33.0	
CO_2 content of arterial blood, *vol. per cent*				33.4
				33.6
CO_2 " " venous " " " "				43.1
				42.6
Difference between arterial and venous CO_2, *vol. per cent*				9.4
O_2 capacity of blood, *vol. per cent*				18.3
O_2 content of arterial blood, *vol. per cent*				18.0
O_2 " " venous " " " "				3.2
O_2 consumption, *vol. per cent*				14.8
O_2 saturation of arterial blood, *per cent*				98
O_2 " " venous " " "				18
Respiratory quotient of blood				0.64

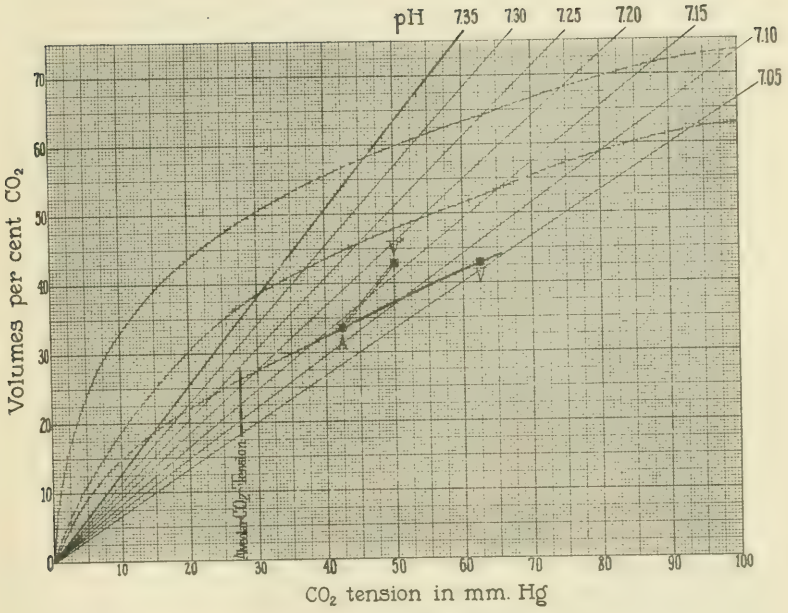
pH
7.35
7.30
7.25
7.20
7.15
7.10
7.05
Volumes per cent CO_2
0
10
20
30
40
50
60
70
80
90
100
Alveolar CO_2 Tension
CO_2 tension in mm. Hg

CHART 12.

Chart 13.

Case 13. M. C. Bronchial asthma with severe emphysema. Male, age 40 years, single, hospital orderly.

Complains of severe dyspnea and cough. Has been admitted to the hospital several times. Looks acutely distressed. Is sitting up in bed. Respirations are rapid and labored, with prolonged, wheezing expiration. Most intense cyanosis of head and extremities, which are a deep purple. Veins of neck engorged. Lungs show boardy resonance everywhere. Expiratory breath sounds prolonged, high pitched, and wheezing. Rhonchi and râles of all kinds heard all over chest. Heart: apex and borders of dulness not made out. Sounds distant. No murmurs made out. Pulse about 100.

Experiment 1. May 12, 1920.

Alveolar CO_2 before arterial puncture, *mm*.				39.8
				44.1
				41.2
" CO_2 after " " "				40.9
CO_2 absorption curve:				
CO_2 tension, *mm. Hg*.	61.9	15.1	75.1	39.6
CO_2, *vol. per cent*.	57.0	32.2	56.9	48.7
	56.3	31.0	58.2	50.1
CO_2 content of arterial blood, *vol. per cent*.				58.4
				56.7
CO_2 " " venous " " " "				63.9
				62.5
Difference between arterial and venous CO_2, *vol. per cent*.				5.7
CO_2 capacity of venous plasma (51.2 mm. Hg), *vol. per cent*.				74.5
O_2 " " blood, *vol. per cent*.				21.3
O_2 content of arterial blood, *vol. per cent*.				17.2
O_2 " " venous " " " "				11.0
O_2 consumption, *vol. per cent*.				6.2
O_2 saturation of arterial blood, *per cent*.				81
O_2 " " venous " " "				52
Respiratory quotient of blood.				0.92

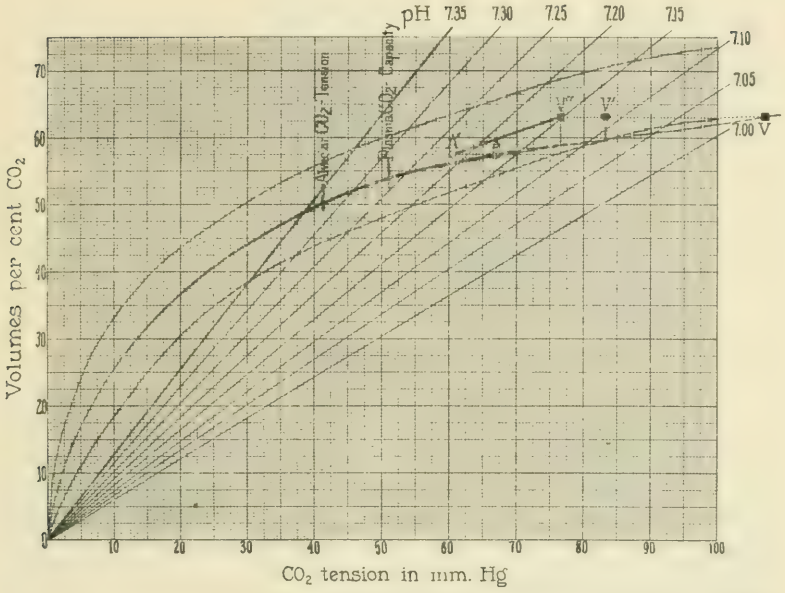

CHART 13. V″ represents the venous CO_2 tension corrected for oyxgen unsaturation, using the value of 0.414 for K (see text).

Additional Protocols.

Case 6. G. B. Paroxysmal tachycardia. Male, age 32 years, single, cook. Acutely ill. Some dyspnea, orthopnea, and cyanosis. Edema of both ankles. Signs of moderate amount of fluid in the right pleural cavity and in the abdomen. Liver enlarged. Temperature about 103° F. Pulse regular, rate about 180. Heart enlarged in both directions, but without signs of a valvular lesion.

Condition did not respond to treatment and patient died suddenly 6 days after the experiment here reported.

Experiment 1. Mar. 24, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	78.7	47.2	11.6
CO_2, *vol. per cent*	61.1	49.1	27.4
			26.4

CO_2 content of venous blood, *vol. per cent* 54.8
O_2 capacity of blood, *vol. per cent* 21.7
O_2 content of venous blood, *vol. per cent* 5.0
O_2 saturation of venous blood, *per cent* 23

Case 8. E. H. Mitral stenosis and insufficiency. Male, age 39 years, butcher. Looks acutely and chronically ill. Sitting, propped up in bed, with considerable dyspnea and orthopnea, pallid, cyanotic, and in acute distress. Edema of both lower extremities, abdominal wall, and back. Double hydrothorax. Moderate ascites. Very large, pulsating liver.

Temperature about 100. Pulse absolutely irregular, rate slow as the result of digitalis therapy.

Heart enlarged to the right and left, with systolic and diastolic thrill and shock, maximum over the midcardiac area. Auricular fibrillation. Patient died 2 days after the experiment here reported.

Experiment 1. Mar. 10, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	16.0	34.8	69.5
CO_2, *vol. per cent*	19.0	46.2	59.2
			61.1

CO_2 content of venous blood, *vol. per cent*..... 51.1

CO_2 capacity of " plasma (44.0 mm. Hg) *vol. per cent*... 64.0

Case 9. P. O. S. Syphilitic aortitis. Aortic insufficiency. Male, age 49 years, single, laborer. Looks acutely and chronically ill. Marked dyspnea and orthopnea with irregular respirations. Moderate cyanosis. Edema of lower extremities, back, and abdominal wall. Signs of fluid in both pleural cavities. Liver very much enlarged. Temperature 100. Pulse regular, rate 90, collapsing in type. Blood pressure: systolic 140, diastolic 50. Heart very much enlarged, especially downward and to the left. Soft, systolic and loud, buzzing, diastolic murmurs, maximum over the base of the heart. Diastolic murmur accompanied by a thrill.

Wassermann ++++.

Patient died 3 weeks after the last experiment without having left the hospital.

Experiment 1. Mar. 9, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	66.8	59.9	20.6
CO_2, *vol. per cent*	63.9	60.7	39.0
	65.4		39.7

CO_2 content of venous blood, *vol. per cent*..... 62.1

CO_2 capacity of venous plasma (51.1 mm. Hg), *vol. per cent*.. 74.2

Experiment 2. Mar. 23. Continues to grow worse. Hydrothorax increasing. Irrational. Dyspnea is less, possibly because of morphine, but respirations are more irregular. Considerable cyanosis.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	(26.4)	93.7	51.8
CO_2, *vol. per cent*	42.8	65.8	52.5
	42.8		

CO_2 content of venous blood, *vol. per cent*..... 56.9

O_2 capacity of blood, *vol. per cent*..... 22.3

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III. THE CARBON DIOXIDE ABSORPTION CURVE AND CARBON DIOXIDE TENSION OF THE BLOOD IN SEVERE ANEMIA.

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(Received for publication, December 2, 1920.)

Carbon Dioxide Absorption Curve in Severe Anemia.

An analysis of the CO_2 absorption curve of normal blood has been made in Paper I of this series (1). In the course of the investigation we had occasion to study the blood of a case of pernicious anemia and found such marked variation from the normal in the shape and character of the absorption curve that we were stimulated to study the bloods of other cases of anemia as they presented themselves in the wards. We later found that the CO_2 absorption curves from the blood of one case of pernicious anemia and from one case of moderate secondary anemia had been constructed in 1917 by Hasselbalch (2) who used them as collateral evidence in his argument concerning the true nature of the supposed acidosis of newly born children. In this paper we wish to present the absorption curves of several patients with varying degrees of anemia, to discuss the factors which may cause the curve of anemic blood to differ from the normal, and finally to show the bearing of the findings upon the respiratory mechanism and particularly upon the dyspnea of severe anemia.

The methods employed have been described in detail in Paper I. The absorption curve of fully oxygenated blood and the CO_2 content of venous blood have been determined. Upon three of the patients arterial puncture was performed and the CO_2 content of arterial and of venous blood was ascertained. The percentage of hemoglobin was obtained in all cases by the oxygen capacity method of Van Slyke (3). In one case the alveolar CO_2 tension was also determined.

TABLE I.

Subject.	Date.	Tension of CO_2. (1)	CO_2 absorbed. (2)	Venous CO_2 content. (3)	Arterial CO_2 content. (4)	CO_2 capacity of plasma. (5)	Venous oxygen content. (6)	Arterial oxygen content. (7)	Oxygen capacity. (8)	Hemoglobin. Haldane scale. (9)	Diagnosis and remarks. (10)
	1920	*mm. Hg*	*vol. per cent*	*vol. per cent*	*vol. per cent*	*mm. Hg*	*vol. per cent*	*vol. per cent*	*vol. per cent*	*per cent*	
Jas. M.	June 10	0.1	45.60	61.28	57.93		0.54	2.92	3.41	18.9	Probable pernicious anemia, male, age 62. Red blood count 710,000. Pulse 88–120. Respirations 18–28. Temperature 97–99°.
			45.60	61.08	57.34				3.28	17.7	
		39.8	58.12								
			59.66								
		78.4	67.38								
			65.90								
C. P.	May 28	24.0	47.30	55.18	52.24		1.55	4.37	4.34	23.1	Pernicious anemia, male, age 55. Red blood count 1,000,000. Pulse 108–112. Respirations 24–28. Temperature 100–101°.
			48.34	54.50	51.55						
		46.8	55.59								
			55.87								
		93.1	63.00								
			64.60								
R. H.	June 10	30.2	46.00	52.08	50.87		0.00	4.76	4.36	23.5	Gastric carcinoma, female, age 44. Red blood count 2,300,000. Pulse 80–104. Respirations 20–32. Temperature 99–102°.
		47.9	51.90	53.43	50.47						
			55.12								
		82.2	60.13								
			61.27								

A. B.	Mar. 16	18.0	51.10	63.99		47.54			6.17	33.3	Pernicious anemia, female, age 47. Red blood count 1,500,000–1,000,000. Pulse 120–128. Respirations 20–24. Temperature 98–102°.
		46.3	64.60	63.91					5.76	31.1	
			60.89								
		80.4	70.00								
	Apr. 1	20.6	48.35						4.80	25.90	
		52.2	58.10								
		91.0	65.10								
E. S.	Mar. 3	6.4	33.52	46.77		33.78	3.66		6.90	37.4	Chronic nephritis, hypertension, and uremia, female, age 22. Red blood count 4,000,000. Pulse 84–108. Respirations 20–28. Temperature 98–99.2°. Blood pressure: systolic 190, diastolic 110.
			33.15						6.45	35.4	
		30.5	44.80								
		53.6	50.67								
			52.08								
C. A.	Mar. 22	25.8	61.40						9.88	53.3	Gastric carcinoma, female.
		38.8	69.80								
		61.0	74.60								
N. B.	Mar. 15	7.1	31.60	60.13		45.26			10.08	54.7	Pernicious anemia, female, age 53. Red blood count 2,700,000. Pulse 92. Temperature 98–103°.
			32.27			45.47			9.61	52.2	
		42.2	53.81								
			52.95								
		71.9	63.46								
			63.18								

The cases upon which this study is based include three patients with pernicious anemia, one with a severe anemia probably pernicious, two suffering from gastric carcinoma, and one from chronic nephritis. A protocol of the combined data of all observations is given in Table I. In Column 1 are included the tensions of CO_2 to which the blood was exposed and in Column 2 the volume of CO_2 absorbed at each tension is given. From these data the CO_2 absorption curves were constructed. The other columns of the table are self-explanatory.

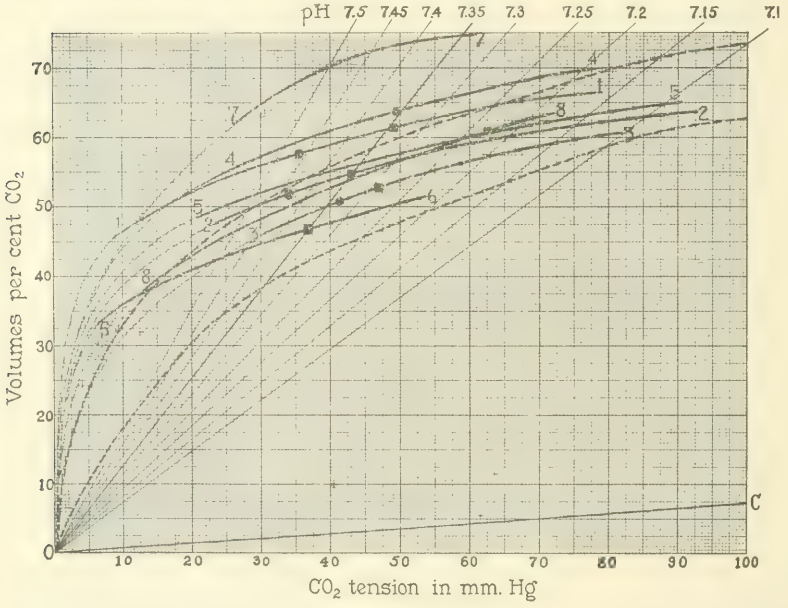

Fig. A. Comparison of CO_2 absorption curves of blood in severe anemia with curves of normal blood.

Solid curved lines: curves from blood of anemia. 1. Jas. M., 18 per cent hemoglobin. 2. C. P., 23 per cent hemoglobin. 3. R. H., 23 per cent hemoglobin. 4. A. B., Mar. 16, 1920, 32 per cent hemoglobin. 5. A. B., Apr. 1, 1920, 26 per cent hemoglobin. 6. E. S., 36 per cent hemoglobin. 7. C. A., 53 per cent hemoglobin. 8. N. B., 53 per cent hemoglobin.

Broken curved lines: limits of dissociation curves from blood of normal persons.

Straight diagonal line *OC* represents the CO_2 in solution and in form of H_2CO_3.

Other diagonal lines represent pH of blood.

● = Arterial CO_2 content.

■ = Venous CO_2 content.

The absorption curves are represented in Fig. A. The solid curved lines are curves of blood from patients with anemia. Each of these is numbered and the numbers, the initials of the patients to which they refer, and the percentage of hemoglobin contained in the blood are given in the legend. The curved broken lines represent the upper and lower limits of the absorption curve for the blood of normal individuals (1). The diagonal, *OC*, gives the amount of CO_2 in physical solution and in the form of carbonic acid for each tension. The other diagonal lines indicate the hydrogen ion concentration in terms of the negative logarithm, pH, of Sörensen (4).

From a superficial survey of the figure it will be seen that the curves of blood in anemia differ markedly from the normal. They are more nearly parallel to the base line. The volume of CO_2 absorbed at low tensions is relatively large while the volume at high tensions is less than normal. In these respects our results are entirely in keeping with those of Hasselbalch (2). The curve of blood from severe anemia resembles the curve of plasma quite as closely as it does that of normal whole blood.

In Fig. B the CO_2 absorption curves of 0.03 M sodium carbonate solution, of 0.1 M sodium phosphate solution, of plasma, and of normal blood have been drawn for the purpose of comparing their slopes with that of the blood of Jas. M., a patient with severe anemia. The curves of phosphate solution and of plasma have been constructed from the figures given by Van Slyke and Cullen (5). The curve of carbonate solution is derived from the formula of Parsons (6).

The difference in the slope of the curves can be explained by the presence and character of the acids in the various solutions. In a solution of sodium carbonate where H_2CO_3 is the only acid, essentially all the alkali combines with CO_2 at low tensions. Below 10 mm. of CO_2 tension the curve is steep, while at all tensions above 10 mm. the curve is flat and parallels the line of physical absorption, *OC*. In plasma, in whole blood, and in the phosphate solutions, all of which contain both H_2CO_3 and other potential acids, the alkali is divided between the acids in proportions depending upon their relative strength and molecular concentration. The amount of alkali which may combine with carbonic acid between any two tensions, and hence the slope of

the CO_2 absorption curve, will depend upon the character and concentration of the other acid substances. For this reason it is important to consider the potential acids which exist in normal blood.

The plasma contains serum proteins which may have acid properties under conditions existing within the body. Attempts

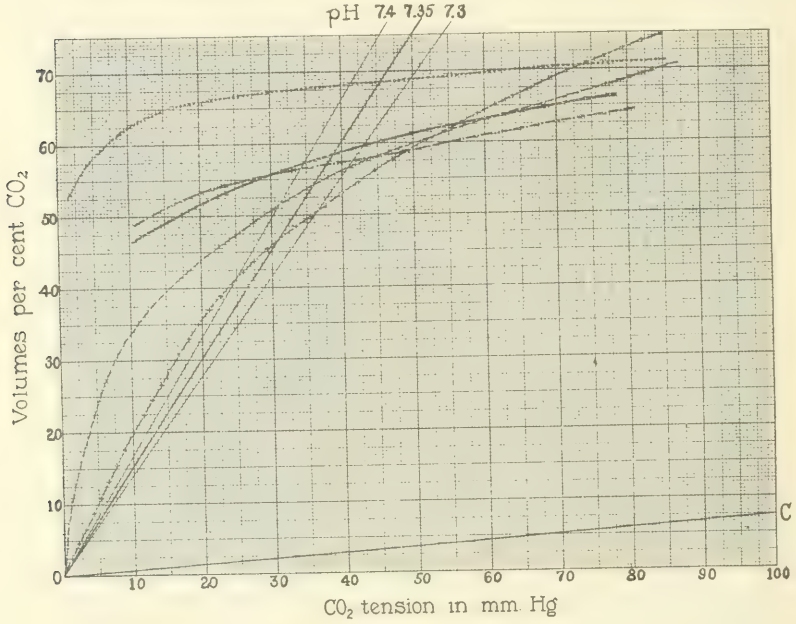

Fig. B. Comparison of curve of blood of severe anemia with other CO_2 absorption curves.

..... = 0.03 M Na_2CO_3 solution.
--x--x--x-- = 0.1 M Na_2HPO_4 solution.
—·—·—·— = Plasma.
---------- = Normal blood.
———— = Blood of Jas. M.; severe anemia.

to measure the magnitude of their acid action have given rise to conflicting results (7–10). The close resemblance between the curve of plasma and that of bicarbonate indicates that their influence is not great under normal conditions. Within the red blood cells there are two substances of potentially acid character, the phosphates and hemoglobin. The influence of the former

cannot be estimated quantitatively. It will be seen, however, that the curve of phosphate solution resembles closely that of normal whole blood. The presence of phosphates might from theory play a considerable rôle in the production of the typical blood curve (11). The action of hemoglobin as a potential acid has been emphasized recently by many investigators (12–15). It has been found to be an amphoteric substance which at the hydrogen ion concentrations existing within the body may have the properties of a weak acid.

In anemia the red blood cells are diminished in number and the reduction is accompanied by a decrease in the concentration of hemoglobin. If the action of hemoglobin as an acid is of importance, a marked reduction in its concentration should produce a flattening of the slope of the curve, which, in the most severe anemias, should resemble the curve of plasma. It has been seen that this actually occurs. The absorption of CO_2 by the blood of Jas. M. with 18 per cent hemoglobin occurs in a manner more like plasma than normal whole blood.

If hemoglobin were the only substance of importance, the slope of the curve should vary directly with the concentration of the pigment. Our results do not show this. The flattening of the curve is detectable only in severe anemia. Curves of blood containing 80 per cent of hemoglobin may have as steep a slope as those with 120 per cent (1). Careful measurements of the curves have failed to disclose any exact relation between the two phenomena. In this respect our curves are not in accord with those of Hasselbalch, who found the slope of the curve to vary directly with the percentage of hemoglobin. The most striking relation between the factors was apparent at low tensions, below those at which most of our curves were constructed. Hasselbalch's curves indicate that the blood of severe anemia does not lose all its CO_2 at 0 mm. of CO_2 tension. If this should be true, the extrapolations, the dotted portions of the curves in Fig. A, may be misleading.

In our data there is no exact relation between the percentage of hemoglobin and the slope of the absorption curve. Other factors must exert an influence. What these factors may be is, for the present, a matter for speculation only. In anemia plasma constitutes a large proportion of the total blood volume. Under

these circumstances the influence of the serum proteins upon the slope of the curve may vary in the different bloods studied. Straub and Meier (14) presented a plasma curve from a patient with polycythemia which differed from the normal and indeed resembled the curve of normal whole blood. It is possible that differences in color index, variations in the relation of the number of red blood cells to the percentage of hemoglobin, may exert some influence upon the shape of the curve. The curve of E. S. indicates that this factor is not of great importance. Although the blood of E. S. contains 4,000,000 red blood cells per cubic millimeter, the curve is as flat as that of the blood of A. B. with 1,500,000 red blood cells.

TABLE II.

Subject.	CO_2 absorbed at 40 mm. tension.
	vol. per cent
Jas. M.	58.4
R. H.	49.2
C. P.	53.0
A. B.	60.0
	54.2
E. S.*	47.0
C. A.	69.0
N. B.	51.5
Average	56.5
" of normal bloods	48.95

* E. S., a nephritic with edema and reduction of plasma bicarbonate. Omitted in calculation of average.

The slope of the curves of blood in anemia implies that at low CO_2 tensions the content of CO_2 will be relatively high. Furthermore, in anemia, plasma constitutes a large proportion of the total blood volume. Per unit volume, plasma contains more alkali than the red blood cells. This also will have the effect of making the CO_2 content of the blood higher than that of normal blood. That the curve in anemia, however, is not invariably high is shown by the curve of the blood of E. S., a chronic nephritic, whose alkali reserve, measured by the plasma method of Van Slyke, was diminished. The CO_2 content of the blood at the physiologically important tension of 40 mm. is shown in Table II.

The difference between the CO_2 content of arterial and venous blood in the three cases studied is much smaller than is usually observed in normal individuals.

Probably the chief physiological significance of the flat absorption curve of blood in anemia is the information which it gives concerning the combining power of blood between any two CO_2 tensions. A flat curve expresses diagrammatically the fact that the blood which it represents will combine with less CO_2 for a given rise in CO_2 tension and will lose less CO_2 for a given fall in tension.

The comparatively low combining power of blood in severe anemia between the tensions of 40 and 60 mm. is represented in a roughly quantitative way in Table III.

TABLE III.

Subject.	CO_2 content at 40 mm.	CO_2 content at 60 mm.	Difference.
	vol. per cent	*vol. per cent*	
Jas. M.	58.4	63.6	5.2
C. P.	53.0	58.8	5.8
R. H.	49.2	55.9	6.7
A. B.	60.0	66.0	6.0
	54.2	58.7	4.5
E. S.	47.0	51.7	4.7
C. A.	69.0	74.0	5.0
N. B.	51.5	58.4	6.9
Average difference			5.6
" normal difference			6.8

The decreased power of the blood in anemia to absorb or dissociate CO_2 with varying CO_2 tensions implies that changes in hydrogen ion concentration will be greater for each shift in tension. This is shown diagrammatically in Fig. A by the relation of the flat curves of anemia to the diagonal pH lines. The actual changes in hydrogen ion concentration between arterial and venous blood within the body are, however, influenced by other factors. The curves of blood in anemia are higher than the normal. This tends to lessen the effect of the flat curves upon hydrogen ion concentration, a fact indicated in the charts by the divergence of the pH lines as they pass from the origin. At 40 volumes per cent of CO_2 the pH 7.30 and 7.40 lines are

TABLE IV.

Results of the Study of Six Patients with Severe Anemia.

Subject.		Date.	Alveolar CO_2 tension.	Alveolar reaction.	Arterial CO_2 content.	Arterial CO_2 tension.		Arterial reaction.		Venous CO_2 content.	Venous CO_2 tension.		Venous reaction.		Difference between arterial and alveolar CO_2 tension.	Difference between arterial and venous CO_2 content.	Difference between arterial and venous CO_2 tension.	Difference between arterial and venous reaction.
						Uncorrected.	Corrected.	Uncorrected.	Corrected.		Uncorrected.	Corrected.	Uncorrected.	Corrected.				
			(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
		1920	*mm. Hg*	*pH*	*vol. per cent*	*mm. Hg*	*mm. Hg*	*pH*	*pH*	*vol. per cent*	*mm. Hg*	*mm. Hg*	*pH*	*pH*	*mm. Hg*	*vol. per cent*	*mm. Hg*	*pH*
18.	N. B.	Mar. 15								60.1	60.0		7.24					
19.	A. B.	" 16 Apr. 1								63.9	50.0		7.35					
14.	R. H.	June 10			50.7	41.0	41.0	7.34	7.34	52.8	47.0	43.0	7.30	7.33		4.8	2.0	0.01
15.	Jas. M.	May 5			57.6	35.0	35.0	7.47	7.47	61.2	49.0	45.0	7.35	7.38		3.9	10.0	0.09
17.	C. P.	" 28	28.2	7.50	51.9	33.5	33.5	7.44	7.44	54.9	42.5	41.0	7.35	7.37	5.3	3.0	6.5	0.07
16.	E. S.*	Mar. 3								46.8	45.0	41.5	7.28	7.32				
Maximum*.....					57.6	41.0	41.0	7.47	7.47	63.9	60.0	45.0	7.35	7.38		4.8	10.0	0.09
Minimum*.....					50.7	33.5	33.5	7.34	7.34	52.8	42.5	41.0	7.24	7.33		3.0	2.0	0.01

* The values obtained from the experiment on E. S., Case 16, have been omitted from the summary of maximum and minimum values because the anemia in this case was complicated by a severe chronic nephritis with uremia.

separated only about 4 mm. of CO_2 tension. At 60 volumes per cent this difference has increased to 10 mm. of CO_2 tension. This attempt at compensation is, however, counterbalanced by the reduction of the effect of oxygen on the curve. It will be remembered that the curves of Fig. A are those of blood containing oxygenated hemoglobin. The curve of reduced blood is always higher than that of the same blood fully oxygenated. Since the hemoglobin of venous blood is partially reduced, the venous points are not correctly represented on the curves of Fig. A, but should lie on a higher curve. If, as was indicated in Paper I of this series, the effect of oxygenation or reduction of the blood upon the height of the CO_2 absorption curve is a direct function of the hemoglobin, it is evident that the effect of oxygen unsaturation on blood from anemia will be less than on normal blood. The complete oxygen unsaturation of a blood with 25 per cent hemoglobin will increase the height of the absorption curve no more than will a 25 per cent unsaturation of a blood with 100 per cent hemoglobin. The net result of these various factors upon the changes in hydrogen ion concentration between arterial and venous blood is shown in Charts 14 to 17 and in Column 16 of Table IV. In spite of the small difference in carbon dioxide content between arterial and venous blood there is a considerable difference in pH, amounting in Cases 15 and 17 to 0.07. This is partly due to the diminished slope of the absorption curve, but even more to the loss of the oxygen effect. Even complete oxygen unsaturation cannot compensate a carbon dioxide change of more than 1 volume per cent in a subject with only 25 per cent hemoglobin.

Carbon Dioxide Tension and Hydrogen Ion Concentration of the Arterial and Venous Blood.

The hydrogen ion concentration of the arterial blood in the three cases studied lies at or above pH 7.34, in Case 15 (Chart 15) as high as 7.47. Means and coworkers (16) have also found the arterial pH quite high. In Case 17 (Chart 17) the alveolar carbon dioxide tension is correspondingly low, giving an alveolar pH of 7.50. In another case of anemia Means found the alveolar pH to be 7.43. This would indicate a tendency toward an arterial

alkalosis and a ventilation somewhat in excess of that which should be expected from the height of the absorption curve.

Although the arterial pH is in general rather high, the venous pH falls surprisingly close to the 7.35 line. In the four instances in which we have sufficient data to calculate the corrected venous pH the limits of variation are 7.32 to 7.38. In Means' case and our Case 19 it is also evident that the venous pH must be much closer to the average normal than is that of the arterial blood. Of course this may be due only to a peculiar coincidence, but it appears too frequently to pass without speculation.

It is generally stated that the respiratory center is controlled by the hydrogen ion concentration of the arterial blood and, in turn, responds in such a way as to maintain the arterial hydrogen ion concentration constant. It seems more probable, however, that the true controlling factor is the reaction of the tissue fluids in the respiratory center. Presumably this reaction is dependent upon carbon dioxide tension, just as it is in the blood. The carbon dioxide tension of the tissues must, however, always exceed that of the arterial blood and must, during the greater part of the circulation at least, be higher than that of the venous blood. In general it must be much closer to that of the venous blood. If the general tendency of the respiratory mechanism, then, is to maintain the pH of the tissue fluids in the respiratory center constant, one should expect the pH of the venous blood from the center to remain constant rather than that of the arterial blood which passes to the center.

This is not apparent in normal persons because, with a normal concentration of hemoglobin, the effect of oxygen on the carbon dioxide absorption curve renders the pH of arterial and venous blood practically identical.

DISCUSSION.

The influence of these factors upon the mechanism of respiration is apparent. The amount of CO_2 carried from the tissues for each change in tissue tension is less than normal. Unless the blood flow is increased, this will tend to result in accumulation of CO_2 within the tissues. With each increase in CO_2 tension, the hydrogen ion concentration rises with relative rapidity. Further-

more, the same difficulty which the blood has in absorbing CO_2 from the tissues is experienced in dissociating it in the lungs. For a given fall of tension the blood of anemia will dissociate less CO_2 than normal. Unless the ventilation is increased the CO_2 will tend to accumulate in the arterial blood and a vicious circle will be established. There is present in severe anemia a tendency to accumulation of CO_2 in the tissues, a diminished ability of the blood to lose CO_2 in the lungs, and a relatively rapid change in hydrogen ion concentration with any change in the CO_2 tension, all factors which tend to excite the respiratory center and produce dyspnea.

It is not surprising, therefore, to find that in severe anemia hyperpnea is present. It is probably not necessary to draw a causal relation between dyspnea and oxygen want even though the presence of the latter should be established. In regard to the question of oxygen consumption, however, the findings here presented suggest an interesting possibility. Barcroft (17) found that *in vitro* the last portions of oxygen were separated from hemoglobin with great difficulty. It is here shown in Cases 14 and 15 that the last bit of oxygen can be removed during the passage of the blood through the tissues. This has been shown previously by Lundsgaard (18) and others. Barcroft also found that the last portions of oxygen were more readily given off if the hydrogen ion concentration of the solution was increased. It seems possible that the more rapidly changing hydrogen ion concentration of the blood of severe anemia may explain why the last portions of oxygen can be freed during the comparatively brief interval of the passage of the blood through the tissues.

CONCLUSIONS.

1. The CO_2 absorption curves of blood from six patients with severe anemia have been studied. They have been found to have a flatter slope than have the curves of normal blood.

2. This is explained in part by the low percentage of hemoglobin. The flatness of the curves, however, is not exactly proportional to the diminution in the percentage of hemoglobin.

3. The blood of severe anemia has a diminished power of absorbing or dissociating CO_2 with changes of CO_2 tension.

Absorption of CO_2 from the tissues or loss of CO_2 from the lungs is probably accomplished with difficulty.

4. In three cases the hydrogen ion concentration of the arterial blood was determined and found to be relatively low, the pH being as much as 7.47 in one instance.

5. The venous pH was surprisingly constant, varying in four cases between 7.32 and 7.38.

6. In spite of the relatively small difference in carbon dioxide content between arterial and venous blood, the corresponding difference in pH is considerable, reaching 0.07 in two cases. This is due to the flat absorption curve and the loss of the compensating effect of oxygen unsaturation.

7. In severe anemia changes in CO_2 tension produce relatively small changes in CO_2 content and relatively great variations in hydrogen ion concentration. The fault in the CO_2-carrying power and the greater changes in hydrogen ion concentration may explain the dyspnea of anemia.

BIBLIOGRAPHY.

1. Peters, J. P., Jr., and Barr, D. P., *J. Biol. Chem.*, 1920–21, xlv, 489.
2. Hasselbalch, K. A., *Biochem. Z.*, 1917, lxxx, 251.
3. Van Slyke, D. D., *J. Biol. Chem.*, 1918, xxxiii, 127.
4. Sörensen, S. P. L., *Ergebn. Physiol.*, 1912, xii, 393.
5. Van Slyke, D. D., and Cullen, G. E., *J. Biol. Chem.*, 1917, xxx, 289.
6. Parsons, T. R., *J. Physiol.*, 1919–20, liii, 42.
7. Moore, B., McQueen, J. M., and Webster, T. A., *J. Physiol.*, 1919–20, liii, p. xxvii.
8. Milroy, T. H., *J. Physiol.*, 1917, li, 259.
9. Bayliss, W. M., *J. Physiol.*, 1919–20, liii, 162.
10. Campbell, J. M. H., and Poulton, E. P., *J. Physiol.*, 1920–21, liv, 152.
11. Henderson, L. J., *J. Biol. Chem.*, 1920, xli, 401.
12. Parsons, T. R., *J. Physiol.*, 1917, li, 440.
13. Parsons, T. R., *J. Physiol.*, 1919–20, liii, 340.
14. Straub, H., and Meier, K., *Deutsch. Arch. klin. Med.*, 1919, cxxix, 54.
15. Joffe, J., and Poulton, E. P., *J. Physiol.*, 1920–21, liv, 129.
16. Means, J. H., Bock, A. V., and Woodwell, M. N., *J. Exp. Med.*, 1921, xxxiii, 201.
17. Barcroft, J., The respiratory function of the blood, Cambridge, 1914.
18. Lundsgaard, C., *J. Exp. Med.*, 1919, xxx, 147.

CHARTS

EXPLANATION OF CHARTS.

CHART 14.

Case 14. R. H. Gastric carcinoma with severe anemia. Female, age 44 years, married. Looks chronically ill. Somewhat irrational. Well nourished, but shows some evidence of loss of weight. Skin pale and yellowish. Lips pale, with slight cyanotic tinge; similar cyanotic tinge in finger-nails. No signs of dyspnea or hyperpnea while at rest in bed.

Lungs show few, crackling râles at bases, especially on left side. Heart not enlarged. Blowing, systolic murmur and soft, diastolic murmur, maximum over aortic area. Pulse soft, regular, rate about 90. Blood pressure: systolic 150, diastolic 40. X-ray examination showed a small effusion in left pleural cavity. Thoracentesis obtained a small amount of viscid, bloody fluid.

Urine showed occasional trace of albumin, no casts. Specific gravity 1.010 to 1.018.

Non-protein nitrogen of blood 43.5 mg. per 100 cc.

Phenolsulfonephthalein excretion 25 per cent in 2 hrs.

Temperature 100–102° F.

Blood counts:

June 5. Leucocytes 20,000; polymorphonuclear 80 per cent; lymphocytes 5 per cent; large mononuclear 10 per cent; eosinophils 5 per cent.

Erythrocytes 1,200,000. A few normoblasts, but no megaloblasts were found.

June 10. Erythrocytes 2,400,000.

Patient died in hospital and autopsy revealed the presence of gastric carcinoma.

Experiment 1. June 10, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	82.2	47.9	30.2
CO_2, *vol. per cent*	60.1	51.9	46.0
	61.3	55.1	

CO_2 content of arterial blood, *vol. per cent*	50.9
	50.5
CO_2 " " venous " " " "	52.1
	53.4
Difference between arterial and venous CO_2, *vol. per cent.*	2.1
O_2 capacity of blood (24 per cent hemoglobin) *vol. per cent.*	4.4
O_2 content of arterial blood, *vol. per cent*	4.8
O_2 " " venous " " " "	0.0
O_2 consumption of blood, *vol. per cent*	4.8
O_2 saturation of arterial blood, *per cent*	100
O_2 " " venous " " "	0
Respiratory quotient of blood	0.44

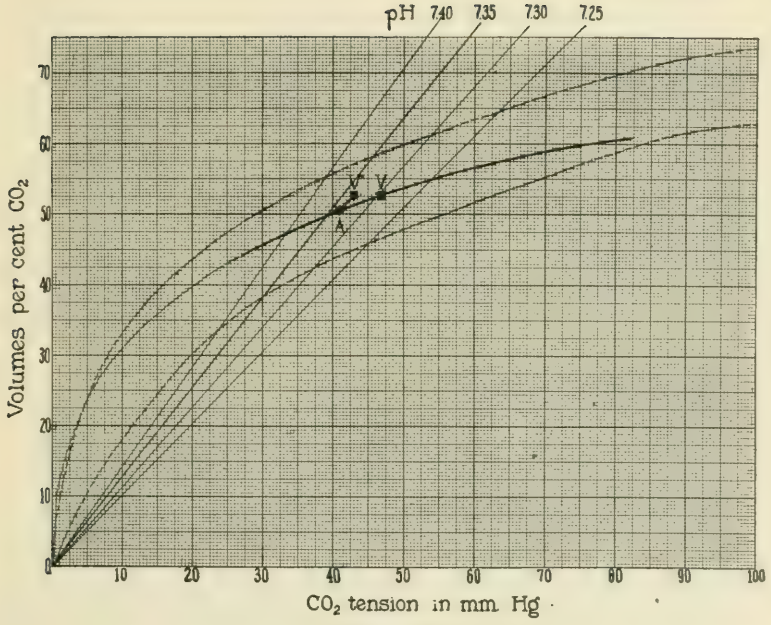
pH 7.40
7.35
7.30
7.25
Volumes per cent CO_2
CO_2 tension in mm. Hg
0
10
20
30
40
50
60
70
80
90
100

CHART 14.

Chart 15 and 16.

Case 15. Jas. M. Severe anemia (probably pernicious). Male, age 62 years, married, fireman. Looks chronically ill. Complains only of pains in the stomach. Mentally sluggish and unable to give any information. Extremely weak. Vomiting greenish brown fluid, streaked with mucus, which contains much bile, 10 per cent acid, no free HCl, and many pus cells. Thin and emaciated, extremely pale. No signs of dyspnea or hyperpnea while at rest in bed. Teeth all gone. Lungs clear. Heart normal. Pulse 58 to 108.

Blood counts:

May 4. Leucocytes 6,200; polymorphonuclear 39 per cent; lymphocytes 59 per cent; large mononuclear 2 per cent; erythrocytes 700,000.

May 6. Leucocytes 2,400; polymorphonuclear 50 per cent; lymphocytes 42 per cent; large mononuclear 2 per cent; erythrocytes 700,000; a few normoblasts and megaloblasts found.

May 8. Leucocytes 3,000; polymorphonuclear 55 per cent; lymphocytes 43 per cent; large mononuclear 2 per cent; erythrocytes 1,900,000; many megaloblasts and a few normoblasts found.

Patient received a transfusion of 630 cc. of citrated blood on May 7. During the night his temperature rose to 103° F., his pulse became very weak, and his respirations shallow and labored. He died at noon the next day. Blood grouping had been carried out with care and no evidence of hemolysis was found.

Experiment 1. May 5, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*.....	39.8	9.1	38.3	78.4
CO_2, *vol. per cent*.....	58.1	45.6	57.7	67.4
	59.7	45.6	57.6	65.9

CO_2 content of arterial blood, *vol. per cent*.....	57.9
	57.3
CO_2 " " venous " " " "	61.1
	61.3
	62.2
Difference between arterial and venous CO_2, *vol. per cent*...	3.9
O_2 capacity of blood, *vol. per cent*.....	3.4
	3.3
O_2 content of arterial blood, *vol. per cent*.....	2.9
O_2 " " venous " " " "	0.5
O_2 consumption, *vol. per cent*.....	2.4
O_2 saturation of arterial blood, *per cent*.....	87
O_2 " " venous " " "	15
Respiratory quotient of blood.....	1.62

Case 16. E. S. Chronic nephritis with severe anemia. Female, age 21 years, married, housewife. Acutely ill. Fairly well developed and nourished. Very pale. Sitting up in bed, with dyspnea, orthopnea, and slight cyanosis. Moderate edema of feet and legs. Lungs show signs of fluid in both pleural cavities. Heart somewhat enlarged, without murmurs. Rate 96. Blood pressure: systolic 190, diastolic 115. Temperature normal.

Urine shows very heavy cloud of albumin, with many casts, many red blood cells, and some pus. Specific gravity 1.006 to 1.011.

Non-protein nitrogen of blood 165 mg. per 100 cc.

Phenolsulfonephthalein excretion about 5 per cent in 2 hrs.

Blood count:

Mar. 2. Leucocytes 19,200; polymorphonuclear 82 per cent; erythrocytes 4,200,000.

Experiment 1. Mar. 3, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	30.5	53.6	6.4
CO_2, *vol. per cent*	44.8	50.7	33.5
		52.1	33.2

CO_2 content of venous blood, *vol. per cent* 46.8
46.8

CO_2 capacity of venous plasma (33.8 mm. Hg), *vol. per cent*.. 49.1

O_2 content of venous blood, *vol. per cent* 3.7
3.7

Experiment 2. Mar. 5.

O_2 capacity of venous blood (35 per cent hemoglobin), *vol. per cent* 6.5

O_2 content of venous blood, *vol. per cent* 3.1

O_2 saturation of venous blood, *per cent* 48

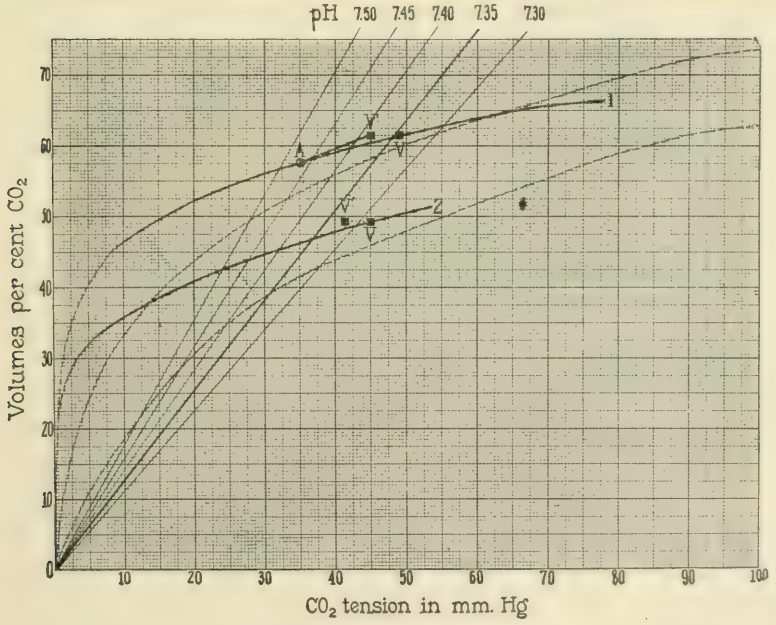

Chart 15 and 16. 1. Case 15.
2. Case 16.

CHART 17.

Case 17. C. P. Pernicious anemia. Male, age 55 years, single, stable worker. Looks chronically ill. Very weak and emaciated. Extremely pale, with lemon-yellow tinge. Some retinal hemorrhages. No signs of dyspnea or hyperpnea while at rest in bed. No cyanosis. Lungs clear.

Heart not enlarged. Blowing, systolic murmur at apex. Pulse regular, 90 to 100. Blood pressure: systolic 145, diastolic 60. Temperature 100–102° F.

Blood counts:

May 24. Leucocytes 3,000; polymorphonuclear 50 per cent; lymphocytes 48 per cent; large mononuclear 2 per cent; erythrocytes 700,000. Many normoblasts and megaloblasts found.

June 2. Polymorphonuclear 60 per cent; lymphocytes 25 per cent; large mononuclear 14 per cent; eosinophils 2 per cent; erythrocytes 1,100,000; many normoblasts and megaloblasts found.

Experiment 1. May 28, 1920.

Alveolar CO_2 before arterial puncture, *mm.*			28.3
			27.8
" CO_2 after " " "			28.6
CO_2 absorption curve:			
CO_2 tension, *mm. Hg*	93.1	46.8	24.0
CO_2, *vol. per cent*	63.0	55.6	47.3
	64.6	55.9	48.3
CO_2 content of arterial blood, *vol. per cent*			52.2
			51.6
CO_2 " " venous " " " "			55.2
			54.5
Difference between arterial and venous CO_2, *vol. per cent*			2.2
O_2 capacity of blood, *vol. per cent*			4.3
O_2 content of arterial blood, *vol. per cent*			4.4
O_2 " " venous " " " "			1.6
O_2 consumption, *vol. per cent*			2.8
O_2 saturation of arterial blood, *per cent*			100
O_2 " " venous " " "			37
Respiratory quotient of blood			0.79

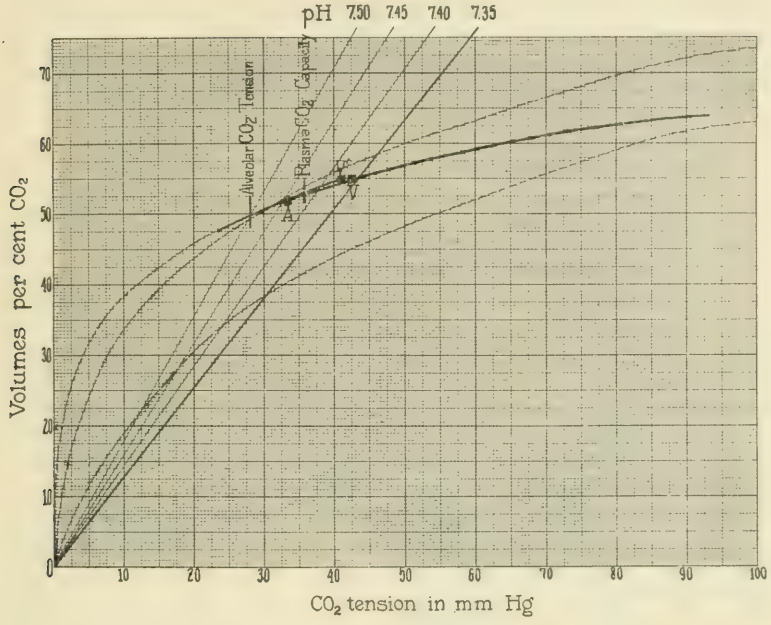

CHART 17.

Additional Protocols.

Case 18. N. B. Pernicious anemia. Female, age 53 years, married, servant. Looks chronically ill. Fairly well nourished and developed, but flabby. Pale, lemon-yellow color. Small hemorrhagic spots in roof of mouth, retinal hemorrhages, and purpuric spots on extremities. No dyspnea or visible hyperpnea while patient is at rest in bed. Lungs clear. Heart slightly enlarged to the left with a soft systolic murmur and accentuation of the pulmonic second sound.

Gastric contents show no free HCl, total acid 25 per cent, no blood. Stools show no gross or occult blood. Gastrointestinal examination by means of x-ray reveals a prepyloric filling defect persisting throughout examination, but no definite evidence of carcinoma.

Temperature varied between 99 and 103. Pulse about 90. Urine showed occasional trace of albumin and a few granular casts; specific gravity 1.006 to 1.015.

Blood counts:

Mar. 11. Leucocytes 5,600; polymorphonuclear 40 per cent; erythrocytes 2,200,000; no nucleated red blood cells.

Mar. 17. Erythrocytes 2,700,000.

Experiment 1. Mar. 15, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	71.9	7.1	42.2
CO_2, *vol. per cent*	63.5	31.6	53.8
	63.2	32.3	53.0

CO_2 content of venous blood, *vol. per cent* 60.1

CO_2 capacity of venous plasma (45.4 mm. Hg), *vol. per cent*.. 66.0

O_2 " " " blood (54 per cent hemoglobin), *vol. per cent* 10.1
9.6

Case 19. A. B. Pernicious anemia. Female, age 47 years, single, housewife. Looks chronically ill. Slightly emaciated, very pallid, with lemon-yellow color. Petechial hemorrhages on hard palate. No signs of dyspnea or hyperpnea while lying quietly in bed. Thyroid distinctly enlarged. Lungs clear. Heart slightly enlarged to left, with soft, systolic murmur at base, not transmitted. Pulse rapid. Spleen not felt.

Gastrointestinal x-ray examination reveals no evidence of new growth. Urine shows moderate amount of albumin, no casts. Specific gravity 1.015 to 1.021. Temperature 99–102° F.

Blood counts:

Mar. 16. Erythrocytes 1,500,000.

Apr. 1. Erythrocytes 1,000,000.

Experiment 1. Mar. 16, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	80.4	46.3	18.0
CO_2, *vol. per cent*	70.0	64.6	51.1
		60.9	

CO_2 content of venous blood, *vol. per cent* 63.8
64.0

CO_2 capacity of venous plasma (47.5 mm. Hg), *vol. per cent*.. 69.1

O_2 " " blood (26 per cent hemoglobin), *vol. per cent*. 6.2
5.8

Case 20. G. A. Gastric carcinoma with anemia.

Experiment 1. Mar. 22, 1920.

CO_2 absorption curve:

CO_2 tension, *mm. Hg*	61.0	25.8	38.8
CO_2, *vol. per cent*	74.6	61.4	69.8

O_2 capacity of blood (53 per cent hemoglobin), *vol. per cent*. 9.9

Extracted from the American Journal of the Medical Sciences
April, 1920, No. 4, vol. clix, p. 540.

THE SIGNIFICANCE OF YELLOW SPINAL FLUID.

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The occurrence of a yellow spinal fluid is sufficiently rare as to excite interest and sufficiently common to merit a brief consideration of its significance. The true syndrome of Froin[1] consists in (1) a spinal fluid which coagulates at once or upon standing—the consistency of the clot varying, but often so tenacious as to permit one to invert the tube; (2) a yellow coloration or xanthochromia; (3) a marked increase in cells and albumin. Froin[2] and all others who have studied this condition are agreed that the coloration is due to the presence of blood pigments chiefly bilirubin and the increased coagulability to an increase in fibrin. We shall not attempt to review the causative factors, mechanical and clinical, that bring about this departure from the usual pathological findings in spinal fluids but proceed to a consideration of the conditions in which it is encountered.

In a description of 100 cases Sprunt and Walker[3] state that the majority of cases showing yellow fluid present the complete syndrome but in 96 cases we have only had it occur in six instances. It appears that the true syndrome of Froin represents the highest development of a process in the spinal fluid of which the yellow coloration without the other essentials represents the earliest stage. Our 6 cases that presented the complete syndrome were 2 meningeal hemorrhages, 2 cases of tuberculous meningitis, and 2 of poliomyelitis.

In 95 cases of cord tumors and other chronic surgical conditions of the spinal cord which Elsberg and Rochefort[4] studied at the Neurological Institute, New York City, they found yellow fluid in 14 cases and spontaneous coagulation in 7 cases—a rather high

[1] Gaz. des hôp., Paris, 1903.
[2] Syndrome de Coagulation Massive, Gaz. des hôp., 1908, p. 1587.
[3] Significance of Xanthochromia of the Cerebrospinal Fluid, Bull. Johns Hopkins Hosp., 1907, xxviii, 80.
[4] Xanthocromia and Other Changes in the Cerebrospinal Fluid, Jour. Am. Med. Assn., vol. lxviii.

proportion which would lead me to believe that disease of this kind tends to produce the conditions necessary for the development of the complete syndrome of Froin as stated by Mestrezat[5] to wit: (1) the existence of a closed cavity shut off from the general circulation in which the elements derived from blood accumulate (by transudation or hemorrhage); (2) an alteration (infectious or toxic) of the vessels of the cavity bringing about a transudation or a number of minute hemorrhages. In Dr. Elsberg's series of cases in which yellow fluid occurred, there were ten extramedullary tumors, two gummas, one varicose vein of the cord, and one neuritis of the cauda equina.

Our series of cases, 96 in all, represent the number of instances in which these cases have occurred in nine years of work of the Meningitis Division of the Health Department. There were 5801 fluids so that the percentage of cases in which yellow fluid occurred was about 1.6 per cent. Of these 96 cases, 60 have been tabulated and accompany this paper in the form of a table which is appended. Thirty-six cases were omitted from tabulation because the diagnosis was never confirmed definitely or there was lack of sufficient data. The chief interest of our series of cases lies in the fact that we see almost exclusively acute or subacute types of disease—which probably accounts for the small number of cases in which the syndrome of Froin occurred in all its manifestatins. Our cases were as follows: tuberculous meningitis 40, poliomyelitis 13, cerebral hemorrhage 3, meningeal hemorrhage 1, cord tumor 1, pachymeningitis 1, cerebrospinal meningitis 1.

Yellow fluids occurred in many cases of recovering epidemic meningitis but were omitted from consideration in this paper because the condition did not occur spontaneously but after the administration of serum, which, however, we do not consider the cause of the xanthochromia.

Mestrezat[6] and many of the French writers have pointed out that the occurrence of a yellow fluid is not uncommon in tuberculous meningitis, yet it forms a very striking fact that it occurs in over $66\frac{2}{3}$ per cent. of our cases. Neal and DuBois[7] have already pointed out that yellow fluids occur too in poliomyelitis.

It had long been my clinical observation which is confirmed by these figures that given a patient with meningeal symptoms who on lumbar puncture shows yellow spinal fluid one should be inclined to a diagnosis of tuberculous meningitis or poliomyelitis—this evidence, of course, being by no means conclusive but merely a factor to be considered in the other points of diagnosis which further study of the spinal fluid usually decides.

[5] Le Liquide Cephalorachidien, Paris, 1912.

[6] Same.

[7] The Diagnosis of Poliomyelitis, Am. Journ. Med. Sc., September, 1916.

TABLE OF YELLOW FLUIDS.

No.	Amount, c.c.	Coagulation.	Albumin.	Globulin.	Fehling's.	Cells, per cent.	Diagnosis.
1	60	0	++1 solid	++ solid	+1	+ 95 (polys.)	Tb. meningitis.
2	15	+++	+++++	+++++	+1	++95 (monos.)	Poliomyelitis.
3	15	0	++++	+++	+	+95 (monos.)	Poliomyelitis.
4	10	0	++++	+++	++	+95 (monos.)	Tb. meningitis.
5	5	0	+++	++++	0	+90 (monos.)	Tb. meningitis.
6	8	0	+++	++	N.d.	None (?)	Poliomyelitis.
7	3	0	++	+++	N.d.	+	Tb. meningitis.
8	20	0	+++	+++	N.d.	+90 (monos.)	Tb. meningitis.
9	40	0	+	+	N.d.	Red blood cells	Meningeal hemorr.
10	8	0	+++	+++	N.d.	+95 (monos.)	Tb. meningitis.
11	3	0	++++	++++	N.d.	+95 (monos.)	Tb. meningitis.
12	8	0	+++	++++	+	+60 (monos.)	Poliomyelitis.
13	40	0	+++	+++	0	+50 (monos.)	Tb. meningitis.
14	70	0	+++	++	N.d.	90 (monos.)	Tb. meningitis.
15	10	0	++	N.d.	N.d.	Few cells	Pachymeningitis.
16	5	0	++	+++	N.d.	++	Poliomyelitis.
17	5	0	++++	++++	+1	+90 (monos.)	Tb. meningitis.
18	10	+	++++	++++	+1	+98 (monos.)	Tb. meningitis.
19	40	0	+++1	++++	+	+95 (monos.)	Tb. meningitis.
20	30	0	++++	++++	+1	++90 (monos.)	Tb. meningitis.
21	20	0	++++	++++	+	+90 (monos.)	Tb. meningitis.
22	20	0	++++	++++	++1	+90 (monos.)	Tb. meningitis.
23	30	0	++++	++++	++1	+80 (monos.)	Tb. meningitis.
24	25	0	++++	++++	++1	+95 (monos.)	Poliomyelitis.
25	15	0	++++	++++	+1	+70 (polys.)	Tb. meningitis.
26	10	0	++++	++++	++	+90 (monos.)	Tb. meningitis.
27	25	0	++++	+++++	+	+90 (monos.)	Tb. meningitis.
28	35	0	++++	++++	+1	+90 (monos.)	Tb. meningitis.
29	5	0	++++	++++	++1	+90 (monos.)	Tb. meningitis.
30	5	+	N.d.	++++	−	Few	Meningeal hemorr.
31	2	0	++++	++++	+1	+ Slight +	Tb. meningitis.
32	5	0	++++	+++	+++	90 (monos.)	Cerebral hemorrhage.
33	30	0	+	+	+++	++	E. C. S. W.
34	35	0	++++	++++	+1	+90 (monos.)	Tb. meningitis.
35	20	++	+++++	++++	++	+70 (monos.)	Meningeal hemor.
36	20	0	++++	++++	+	+mod 90 (mon.)	Tb. meningitis.
37	20	0	++++	++++	+	+80 (monos.)	Tb. meningitis.
38	3	..	++++	++++	N.d.	N.d.	Poliomyelitis.
39	20	0	+++	+++1	+++	+60 (monos.)	Poliomyelitis.
40	10	0	++++	++++	+1	+95 (monos.)	Tb. meningitis.
41	20	0	++++	++++	0	+98 (monos.)	Tb. meningitis.
42	5	0	+++++	+++++	+	+89 (monos.)	Tb. meningitis.
43[8]	30	0	++++	++++	+++	Moderate +	Poliomyelitis.
44[9]	25	0	++++	++++	+++	+ monos.	Poliomyelitis.
45[10]	40	0	++++	++++	+	+90 (monos.)	Tb. meningitis.
46	30	0	++++	++++	+	+90 (monos.)	Tb. meningitis.
47	2	0	++++	N.d.	N.d.	+	Tb. meningitis.
48	3	0	++++	+++	+1	+90 (monos.)	Tb. meningitis.
49	10	0	+++	+++	+	+99 (monos.)	Tb. meningitis.
50	20	0	+++	+++1	+	+95 (monos.)	Tb. meningitis.
51	40	0	+++	+++	+++	+90 (monos.)	Poliomyelitis.
52	20	0	+++	++1	+	+mod. 95	Tb. meningitis.
53	15	0	+++	+++	+++	N.d.	Cerebral hemorrhage.
54	10	0	++++	+++	+++	+90 (monos.)	Tb. meningitis.
55	30	0	++1	++1	+1	+50 (monos.)	Poliomyelitis.
56	60	0	+++	+++	+1	+99 (monos.)	Tb. meningitis.
57	15	0	++++	++++	+	+95 (monos.)	Tb. meningitis.
58	15	0	+++	++++	++++	+75 (monos.)	Poliomyelitis.
59	30	0	+++	++	++	+90 (monos.)	Tb. meningitis.
60	30	0	++	+++	+	+99 (monos.)	Tb. meningitis.

[8] Fluid No. 43, gold chloride curve, 1111, 232100.
[9] Fluid No. 44, gold chloride curve, 111, 22332210
[10] Fluid No. 45, gold chloride curve, 111, 2322100.
N.d., not done.

Summary:

Tuberculous meningitis	40
Poliomyelitis	13
Cerebral hemorrhage	3
Epidemic meningitis	1
Pachymeningitis	1
Syringomyelia	1
Meningeal hemorrhage	1
Total	60

The spinal fluid withdrawn in these cases has varied in amount from 3 c.c. to 50 c.c. The color has ranged from the faintest of yellow tints to the deepest canary. The albumin and globulin have been markedly increased in the majority of the cases. The sugar reactions as shown by the reduction of Fehling's solution has varied with the underlying etiological infection. In three instances colloidal gold curves were performed and these are included in the table.

RÉSUMÉ. (1) Yellow spinal fluid occurs in a wide range of diseases of the spinal cord and meninges; (2) the complete syndrome of Froin is comparatively rare in its occurrence; (3) in acute or subacute conditions the presence of yellow fluid strongly suggests the probable diagnosis of tuberculous meningitis or poliomyelitis.

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A CASE OF VON JAKSCH'S ANEMIA OCCURRING IN A CHILD 5½ MONTHS OLD

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In 1889 Von Jaksch described a severe anemia occurring in children. The blood of the patients which he reported had a very low total red cell count with degenerated and nucleated red blood corpuscles. The total white blood cell count was increased. Since that time a number of cases varying much in type have been reported as cases of Von Jaksch's anemia or as anemia infantum pseudoleukemia.

It is probable that in the future the cases ordinarily placed in this group will be divided into a number of different types. As one reads the reports of the cases in the literature one comes to the conclusion that some of the blood counts bear a remarkable likeness to idiopathic pernicious anemia, so-called, while others cannot easily be differentiated from chronic myelogenic leukemia of the myelocytic type, and still others resemble lymphatic leukemia. Out of the seven cases that have been counted in our laboratory since 1903, which have been studied by myself, most of them are indistinguishable from chronic spleno-myelogenous leukemia. On the other hand the case which I am now reporting is more nearly like the pernicious anemia type. The classification of blood diseases, in fact, of any pathological condition, is in a very confusing state, and I will dwell no longer upon it.

A matter of great importance, however, is the etiology of these conditions. It is possible that these severe changes in the spleen, bone marrow and liver may be brought about by some toxic infectious agent. Another factor to take into consideration is that the blood-forming organs of infants are in an unstable state and are more easily incited to abnormal function. Rickets is supposed to accompany this condition more than any other clinical manifestation, in fact the clinician usually makes a diagnosis of rickets in such cases. Malaria, syphilis, tuberculosis, gastro-enteritis and other infections have been considered as etiological factors. The etiology of Von Jaksch's anemia is also one of the questions yet to be solved by medical investigators.

The case in which I am interested was sent to the laboratory for a blood examination on December 28, 1918. The clinical diagnosis by several physicians was sarcoma of the kidneys, but other physicians thought the mass in the left side of the abdomen was the spleen. On looking at the blood smear it seemed to me that the patient must have the so-called Von Jaksch's anemia, and at the autopsy this was verified, since the enlarged mass proved to be the spleen. The mother stated that the mass in the left abdomen of the baby was found by a physician when the child was three months old, as at that time she had consulted a physician because the child was constantly crying. On calling up the physician he stated that he had made a diagnosis of splenic anemia.

When the child entered the Cornell Dispensary the weight at five months was thirteen pounds and four ounces, and in a month he lost one pound. At six months of age the weight was twelve pounds and two ounces. He appeared very bright and alert. The skin was pale, with just the faintest tinge of yellow. There were no signs of rickets. The mass in the left side of the abdomen extended down about three inches below the costal margin and a distinct notch was easily palpated.

The blood count at this time was: Hemoglobin 15 per cent. Sahli, red blood cells 1,100,000, color index 1.3, white blood cells 28,000.

Second blood count January 16, 1919. Child born July 4, 1918: Hemoglobin 15 per cent. Sahli, red blood cells 1,428,000, color index 1+, white blood cells 39,000, after subtracting nucleated reds.

Red Cells

Anisocytosis, very marked.
Poikilocytosis, very marked.
Polychromatophilia, marked.
Granular basophilia, slight.
Normoblasts 321.
Megaloblasts 6.

Differential Count

	Per Cent.
Polynuclear leucocytes	34
Transitionals	24
Lymphocytes	23
Large mononuclears	9
Eosinophiles	1
Mast cells	1
Myelocytes	2
Leucoblasts	4
Turk's stimulation form	2
	100

Dividing nucleated reds and Jolly bodies present.

Two examinations of the urine showed nothing abnormal, except a trace of albumin. Blood and bile pigments were absent. The mother's Wassermann test was negative.

The child was sent to the General Memorial Hospital for treatment with radium, which was used only once. Several days after this it died of pneumonia and permission was given to do a partial autopsy through the persuasion of Dr. Mulcahy. The mass in the left abdomen proved to be the spleen which weighed 120 grams and measured 11 by 5.5 centimeters. The capsule was smooth, thin and glistening. Seen through the capsule the organ presented a diffuse reddish-purple appearance. The surface of the organ presented numerous pinpoint-sized, capsular stipplings. On section the organ cut readily. The substance was abundant and deep purple-red in color. The Malpighian corpuscles could not be seen. The cut end of the vessels in the splenic substance was not noticeably thickened.

Examination of the microscopical section showed that the capsule was about normal in thickness. The characteristic appearance given by the Malpighian corpuscles was absent since they were not distinguishable. There was an increase in the connective tissue stroma. Throughout the section there were foci of rather large cells, some of them with pycnotic nuclei and very reddish staining cytoplasm, probably nucleated red cells. The other cells had large vesicular nuclei and these did not show enough histological structure (because of the autolysis which had taken place) to be identified with certainty. They may be either myelocytes or myeloblasts. These are probably centers of myeloidization. Surrounding each focus was an area which was somewhat devoid of cells. The spleen probably belongs in the third group as classified by Dr. Stillman.

The left kidney was normal in size and position. The liver was pale and projected 32 cm. below the ribs on the right nipple line and 25 mm. below the costal margin in the midline. Permission to go any farther with the autopsy was not obtained.

Little can be written as to the treatment of these cases. Some

of the patients recovered spontaneously. Stillman (1) reported cases from whom the spleens were removed and of these two recovered. Dr. W. S. Stone, of the General Memorial Hospital, wrote me that patients treated with light applications of radium were temporarily improved at least.

I wish to express my thanks to Dr. Thomas A. Mulcahy, through whose efforts we were enabled to study this case.

Bibliography

1. *Am. Jour. Med. Sc.*, 1917, cliii, 218.

Discussion:

Dr. Ewing: I think it would be interesting if one could find in the spleen some source of the enormous number of nucleated red cells found in the circulation, but I cannot see that the cells in the spleen are hemoglobin-holding. Of course some nucleated red cells contain very little hemoglobin, so that, considering the rather poor fixation of the spleen, it is possible that many hemoglobin-holding cells would not be recognizable on staining. But on the whole I think if the spleen had contained any considerable number of nucleated reds they could have been recognized. This leaves practically only the bone marrow as the source. The liver is noted as being enlarged. The only case I have seen at autopsy of uncomplicated von Jaksch anemia was one I reported years ago, and in that the capillaries of the liver were the seat of numerous foci of what Dr. Thro would call leukoblasts. I do not feel that without new data I can engage in any speculation regarding the nature of von Jaksch anemia, but still, perhaps it is safe to refer to an opinion formed many years ago to the effect that von Jaksch anemia is probably an exhibition of the very unstable regenerative efforts of the blood forming organs in infants, and that the enormous increase in the nucleated red cells is to be interpreted as similar to that seen in adults on a small scale in primary anemia. I do not see that there has been any new evidence brought forward since that time which would confirm or dispose of that theory.

Dr. Moschcowitz: May I ask from what the child died?

Dr. Thro: The doctor who took care of it in the last days made the diagnosis of bronchitis and pneumonia.

Dr. Moschcowitz: The question of the prognosis of von Jaksch's anemia has always interested me. I have no idea as to how many of these cases recover, and how many die. This is another instance of an uncommon chronic disease in which we see only the intermediary stage, never the beginning, and only very rarely the end.

SOME UNUSUAL BLOOD CELLS IN DISEASES OF BONE MARROW ORIGIN.*

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In making a routine examination of the blood of a dispensary patient, the examination of the stained smear brought to light such an unusual blood picture that it seems of interest to publish the case, with additional remarks on unusual cells found in certain diseases of the blood. The smears, from which the drawings were made, were stained with Hastings' modification of the Nocht-Jenner stains.

The study of the diseases of the blood has attracted many investigators, with the result that there are many classifications. Further studies of blood cells with modern staining methods and the use of the oxydase reaction warrant the changing of the names previously used; an excellent illustration of this being the misnomer, *acute lymphatic leukemia*. This name has been applied because of the predominance of cells which in certain respects resembled lymphocytes, and which were called by Ehrlich "large lymphocytes." Now it is believed that these cells are of marrow origin and they are called myeloblasts (see Plate, Figs. 12, 13). It is believed that these cells do not arise from the lymph system, although true lymphocytes may arise from the marrow. Also, as further proof of their marrow origin may be mentioned the demonstration, by the oxydase reaction, of granules in the cell body. This is considered evidence of their origin from the bone marrow.

It is interesting to think of the changes that occur in the blood-forming organs as the result of the stimulation by various so-called toxic substances. And it seems to me that eventually all the blood diseases will be found to be traceable

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to a response by the hemopoietic organs to the stimulating action of some substance elaborated by the presence in the host of some parasite, microscopical or otherwise. It may be that it will yet be found that B. aerogenes capsulatus, for example, is the causative factor in pernicious anemia, and I predict that as our knowledge widens in regard to various ultra-microscopical forms and of the reaction of the living organism to various toxic products, that the etiology of pernicious anemia will be elucidated. Before the discovery that the extremely severe pernicious type of anemia, due to the dibothriocephalus tapeworm, was caused by the presence of that parasite, patients suffering from its presence were considered to have an idiopathic pernicious anemia.

Keeping this example constantly before us, it is necessary to seek diligently in patients with pernicious anemia for some etiological factor, the discovery of which and its elimination, if possible, might result in the cure of the patient. The idea that these blood diseases are comparable to tumors should not discourage us, since studying the former might result in also throwing some light on the etiology of the latter.

To recur to the idea of the response of the hemopoietic organs to different stimuli, what is more wonderful than the remarkable increase in the relative proportion as well as in the absolute increase of eosinophilic cells in trichinosis? The stem eosinophile cells must be enormously stimulated and the discharge of such cells into the blood stream follows. On the other hand, the stimulus of bacterial action, as in pneumonia or staphylococcus infection, results in the production of polynuclears and of their precursors, the transitional cells (Plate, Fig. 19), which appear in the blood stream before their development into polynuclears. The stem cells of the two types must be in extremely intimate contact and are illustrations of the highest type of selective activity. It is barely possible that all these phenomena may be explained as a chemotactic activity. In some obscure way the reaction of the polynuclear cells is also connected with the immune system of the organism, as has been noted

by students of the blood in pneumonia and is expressed in the monograph on pneumonia of the Rockefeller Institute.

The patient to whom I have previously referred was a man thirty-eight years of age. As he walked into the laboratory to get his blood examined, I noticed that he appeared weak, and although he seemed to be in good flesh, his skin was yellowish and flabby. The patient was white, born in the United States, and was a truck driver. He gave a history of having had an excessive cough for three weeks which bothered him mostly at night. He did not raise any mucus while coughing, and it caused him pain referable to the region over the sternum. Since the cough started he had also been troubled considerably with dyspnea. He complained of being dizzy all the time. Since the cough began he had vomited every morning before breakfast. Every day he had chills of about five minutes' duration. He perspired every night. In the three weeks' interval he had lost fifteen pounds in weight. The patient also complained of frequent micturition.

His general health had been good and the only disease that he remembered that he had had was whooping-cough. One sister had died of tuberculosis. He denied having had syphilis and the taking of alcohol in any form. He smoked about 15 cigarettes a day.

Casually, the patient looked well nourished. The facies was anxious. The skin was yellow with the scleræ yellow, and the tongue was pale and flabby.

The examination of the heart brought out a systolic murmur at the base of the heart, and the same murmur could be heard at the apex, but it was not transmitted. There were numerous coarse râles throughout the chest.

In examining the abdomen the stomach was found to be distended. There were suggestive signs pointing to a small amount of fluid in the abdomen. The spleen was palpated two and one-half inches below the costal margin.

The reflexes were normal.

Laboratory tests: Urine, cloudy, pinkish in color, and highly acid. Sp. gr. 1020. There was not an excessive amount of indican. The albumin and reduction tests were negative. In the sediment there were amorphous urates, uric acid crystals, but no cells, casts, red blood corpuscles, nor leucocytes. In fact, the urine did not give any idea of excessive blood destruction.

The Wassermann reaction was negative.

Blood examination. — The hemoglobin with the Dare was forty-five per cent. The red cell count was 1,500,000. Index was high, that is 1.5. White blood cells numbered 8,000. This is probably incorrect, because it was found on

examining the smears that there were about as many nucleated red blood cells as there were leucocytes, consequently the latter were probably 4,000 to 5,000 in number.

The red cells showed extensive variations in shape, as shown in Figure 18. There were also great variations in size, as shown in Figures 17 and 19. There was considerable polychromatophilia, as represented in Figures 15 and 16. Various types of granular degeneration were seen, as shown in Figures 14 and 16.

As was stated previously, there was an enormous number of nucleated cells, in fact, in counting three hundred leucocytes an equal number of nucleated red cells was noted down. Nucleated red cells of the three ordinary types were seen, that is, normablasts (Fig. 9), intermediates (Fig. 10), and megaloblasts (Fig. 3). Figure 4 is an example of the cell, called Turck's stimulation form, which we believe occurs in the blood as a result of a mild stimulation of the bone marrow. Some toxic substance absorbed from the intestinal tract, or a bacterial toxin, causes the appearance in the circulatory blood of these Turck's cells, which seem to me to be myeloblasts or very immature leucocytes. We find numbers of them in some cases of lobar pneumonia. I believe some hematologists think they are forms of megaloblasts, and we must confess that it is extremely difficult to separate one from the other. Other forms of megaloblasts found in pernicious anemia are shown in Figures 1, 2, 5, 6, 7. Figures 5, 6, 7 represent megaloblasts in various stages of cell division. Figure 5 represents the cell in the so-called cell plate stage. Figure 6, the chromosomes have parted, and in Figure 7, the chromatin has gathered at the poles. Figure 7 is interesting in that there are present at the periphery of the cell two small bodies which resemble the polar bodies seen in the ova of Ascaris, when they are maturing in the ovary of the worm. Figure 8 is one of the many lobulated normablasts not infrequently found.

But the cells that interested me and made me think that the case was not one of ordinary pernicious anemia are figured in Figures 11, 12, 13. At first sight they appear to be

large lymphocytes, and they are probably the cells which were called large lymphocytes by Ehrlich. But it is these cells, which on the application of the oxydase reaction are found to contain granules, and therefore they are of marrow origin and also differ in the following particulars from the true lymphocytes. In size they all run much larger than lymphocytes. All the cells possess much more cytoplasm, which makes the cell body much larger than that of lymphocytes; also the cytoplasm does not stain so deeply with the methylene blue element of the stain.

In the cytoplasm there were a number of red-staining bodies, some like irregular granules,[1] and others were distinctly rod-shaped. The idea that the latter might be some form of parasite has been considered. The nucleus is stained reddish purple and is round or elliptical, usually, but forms were found in which the nucleus was distinctly transitional in type, like that of the traditional cell shown in Figure 20.

The nucleus in many of the cells contained two or more nucleoli, readily seen in Figure 11. These cells are very distinct and can be readily separated from lymphocytes, Turck's stimulation forms, and megaloblasts. As soon as the smear was examined it was recognized that the case was not one of typical pernicious anemia, because of the presence of these cells.

The cells correspond to the descriptions of Naegeli's myeloblasts or Turck's lymphoid marrow cells. It is believed that they arise from the bone marrow, and that they belong to the type of cells which are the predominating cell in so-called acute lymphatic leukemia, therefore it is better to call such cases *acute myeloblastic leukemia*. It was thought by several hematologists who looked at the slides that the patient was in that phase of pernicious anemia called Von Leube's leukanemia. The differential cell count was: Polynuclears, 26 per cent; transitionals, 16.3 per cent; lymphocytes, 43.3 per cent; large mononuclears, 11 per cent; myeloblasts, 3.3; a few Turck's stimulation forms were noted.

The presence or absence of nucleoli, it seems to me, is sometimes the result of varied manipulation of the stain. Nucleoli are more evident in old smears that have been mounted in balsam for a considerable time. The same can be said to a certain extent of granules in the cytoplasm, for example, occasionally lymphocytes possess a few dark granules. The presence or absence then of nucleoli or azur granules I am convinced cannot be used to separate myeloblasts from Turck's lymphoid marrow cells, and I am inclined to adhere to the name myeloblasts, whether or not nucleoli or granules are present. But the granules in the myeloblasts, found in the blood of the patient that I have just discussed, were very distinct in the freshly stained preparations.

In an experience extending over seven years in which many abnormal bloods were examined, only one other case with pernicious anemia had a blood picture like the one described. This was a hospital patient and although there were many myeloblasts present, none of them had such distinct rod-shaped granules. These patients then had all the blood changes of pernicious anemia with the addition of cells characteristic of those found in so-called acute lymphatic leukemia, and it seems such are correctly designated by calling them cases of leukanemia.

As to the origin of some of these cells it seems to us that the myeloblasts arise from a marrow stem cell or hematoblast that is separate from the cells which form red blood cells, although we all know that in the early embryonic life all blood comes from mesenchymal cells.[2]

From the myeloblasts probably arise large mononuclear cells, different kinds of myelocytes and Turck's stimulation forms. In newly created neutrophilic myelocytes and polynuclears the neutrophile granules stain darker with the Hastings' stain. Another change worthy of note is that in newly created eosinophiles, in trichinosis especially, the granules are darker stained and not quite so distinctly globular as are the granules of eosinophile cells found in the normal blood (see Fig. 22).

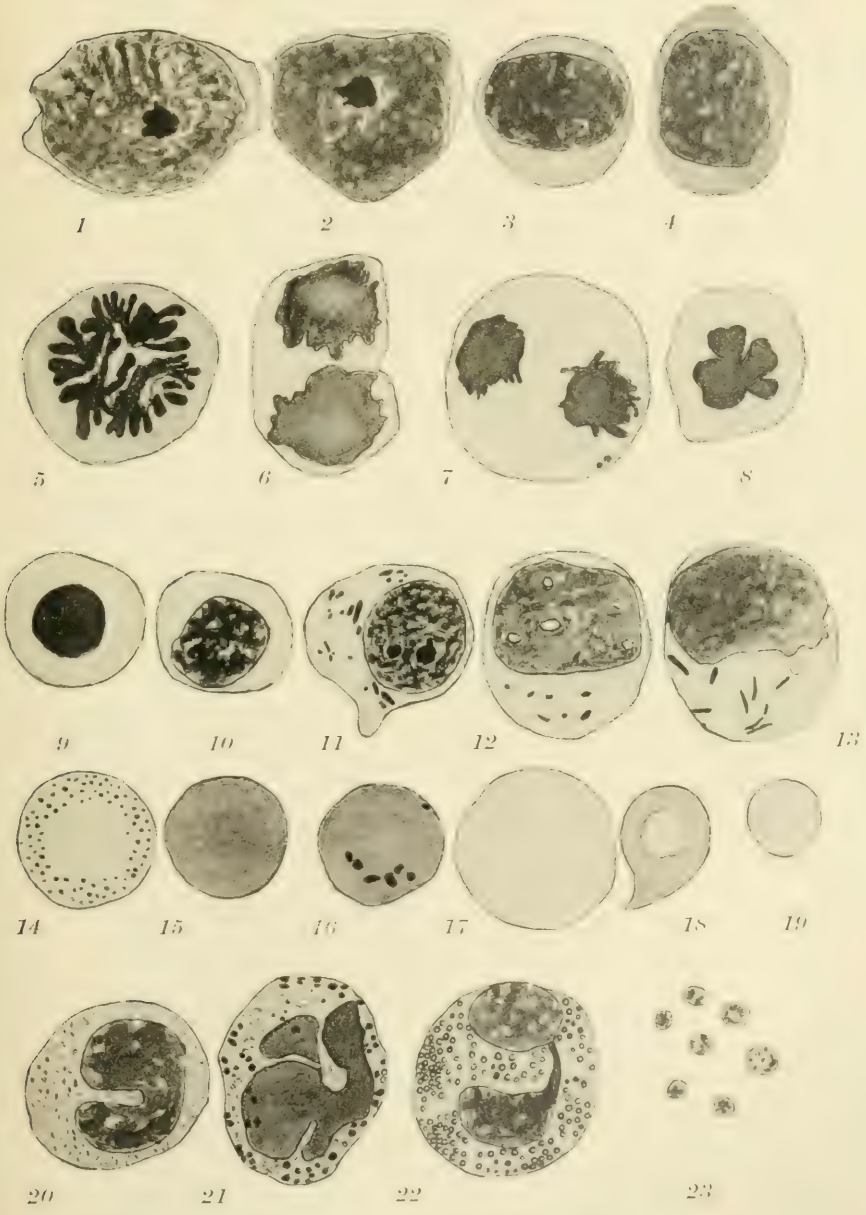
It seems to me, after a study of the marrow of guinea-pigs, that the red blood cells arise in distinct areas, and that they seem to break away from a matrix or syncytium. There are present in the marrow large masses of cytoplasm with a strong affinity for the eosin, and through this mass there are present nuclei characteristic of the intermediate type of normablast (Fig. 10). It seems then that the normablast with the round pyknotic nucleus must be derived from these intermediate cells, but it seems doubtful that true megaloblasts ever develop into normal red blood cells.

The true lymphocytes develop mainly of course from the lymph system, and as was previously stated, do not show granules with the oxydase reaction. We do not attempt to differentiate large and small lymphocytes, believing that, if the smears are perfectly made of extremely thin films of the blood, all the lymphocytes will appear larger with more cytoplasm and paler in hue, while on the other hand the lymphocytes in the thick portions of the smear will appear shrunken with scarcely any cytoplasm showing, and that will be dark in hue.

These rare forms of pernicious anemia characterized by the presence of many myeloblasts, which give the blood picture a slight resemblance to leukemia, are well named *leukanemia*.

REFERENCES.

1. Cowdry. Mitochondria. Internat. Monat. f. Anat. u. Physiol., 1914, Bd. xxxi, Heft. 4/6.
2. Stockard. Am. J. Anat., 1915, xviii, 227; 1915, xviii, 525.



Thro. Blood-cells.

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BACTERIOLOGIC STUDIES IN CHRONIC ARTHRITIS AND CHOREA[1]

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I. BACTERIOLOGICAL STUDIES IN ARTHRITIS

This work was part of a study of chronic arthritis undertaken to determine whether any constant cultural or immunologic streptococcus was associated with the disease. At the outset it was found necessary to define clearly the type of the disease studied on account of the ever changing terminology due to etiologic studies, and consequent changes in classification. For instance, one case of gonorrhoeal arthritis may simulate a case of acute rheumatic fever, and another an arthritis deformans. A complete bacteriologic study is necessary for a proper classification, and the bacteriologic studies in arthritis are by no means yet finished. Therefore any classification now given will have to be changed as the result of subsequent studies. However, so that the type of case studied may be somewhat defined, it may be well to state in a broad way a possible general classification.

ARTHRITIS

Non-bacterial in origin

a. Traumatic
b. Metabolic including gout, acute and chronic
c. Following injection of diphtheria antitoxin and other sera
d. Secondary to nervous diseases, e.g., tabes
e. Associated with certain diseases, e.g., scurvy, hemophilia, purpura, etc.

[1] Presented before the Society of American Bacteriologists, December 31, 1919.

Associated with bacteria in origin

a. Acute rheumatic fever

b. Acute suppurative arthritis, e.g., acute pyogenic joint infection.

c. Chronic suppurative arthritis, e.g, tuberculosis of joint.

d. Acute non-suppurative arthritis, e.g., that acute exacerbation which occurs frequently during the course of a chronic non-suppurative arthritis. These attacks are usually mildly febrile, and present a local picture not unlike that of acute rheumatic fever. The joint involved may be one previously diseased, or may be a newly involved one.

e. Chronic non-suppurative arthritis

1. Syphilitic. This condition is much more common than is recognized and is frequently found complicating other types

2. A type of arthritis probably not representing a disease entity, but rather a group of diseases which have been variously termed:

Arthritis deformans, Virchow
Rheumatoid arthritis, Garrod
Osteo arthritis, Garrod
Rheumatic gout, Fuller
Chronic rheumatic arthritis, Adams
Nodosity of the joints, Haygarth, etc.

The dominant features of this type are the tendency to involve many joints especially the smaller ones, the disposition to the destruction of the articular and periarticular tissues resulting in exostoses and ankylosis, and the usual progressive chronicity of the disease.

It is this latter type that was selected for this study. It remains for investigators to determine by etiologic studies whether this type represents a chronic form of acute rheumatic fever, or whether in this type there is included a group of diseases. Also if a constant bacterium is found associated with the disease, it must be determined whether the arthritis is the result of the activity of the bacteria themselves in the articular or periarticular tissues, or the result of toxines elaborated by these bacteria in some remote focus. This work makes no pretense of clearing up these questions, for the streptococcus studied is not

always found, and it has not been determined that the disease is produced by the inoculation of the streptococcus or its toxins. Further work on this subject is now under way.

The literature of this subject is not satisfactory on account of the variations of classification. Very little bacteriologic work has been done on this type. D. J. Davis (1913) found that in this class of case streptococci could rarely be demonstrated excepting at autopsy, but he did occasionally obtain this organism from the regional lymph glands. E. C. Rosenow (1914) found that by making cultures directly from the glands draining the inflamed joints in 54 cases there could be isolated

	Cases
Modified *Streptococcus viridans*	32
Staphylococcus	5
Bact. mucosum	3
Neisseria catarrhalis	1
Gonococcus	1

Moon and Edwards (1917) in 83 cases of chronic arthritis took blood cultures using the technique described by Rosenow and obtained

	Cases
Negative cultures	58
Non-hemolytic streptococcus	18
Bact. mucosum	3
Diphtheroid bacillus	3
Unidentified	1

In acute rheumatic fever much work with not at all uniform results has been done, notably by Poynton and Paine (1913), Beattie and Yates (1912-13), R. I. Cole (1914), H. K. Faber (1915), Swift and Kinsella (1917), E. C. Rosenow (1914), Moon and Edwards (1917) and others. It is difficult to determine what types of cases have been included in these studies. Very frequently cases of typical chronic deforming arthritis at the outset present the picture of acute rheumatic fever; and acute rheumatic fever may extend for months with a low grade fever relapsing into a severe type for a few hours or days at each new focal extension, and terminating either in death, complete recovery, or recovery with damaged tissues and a tendency to relapse. On account of the frequency of these border line cases, the blood

cultures for the present study were taken from patients who were constantly afebrile excepting for the infrequent attacks of fever, lasting for a short time only, during an exacerbation of the arthritis, and the cultures were not taken at the time of the fever. No case is included in this series that did not have at least three months' history of arthritis. It was purposed to include no case that could possibly be considered as acute rheumatic fever. Likewise no case is included with a history of syphilis or a positive Wassermann reaction, or a history of a recent gonorrhoea or a positive gonorrhoeal fixation test.

The technique of blood culture was the same in all cases:

1. North's medium was used. Heating this medium for sterilization caused different batches of the media to increase in acidity to markedly different degrees. It was found necessary for the development of the streptococcus obtained, to titrate the medium so that after the final heating at the time of planting, the reaction was 0.3 to 0.5 $\frac{N}{10}$ acid, using phenolphthalein as an indicator.

2. Five to ten poured plates were used, and planting was done immediately after taking the blood.

3. The concentration of the blood in the plates was varied, so that the first plate had in it only about 0.3 cc. of blood, and the last 5 to 6 cc. This procedure showed that very often a growth would be obtained in the dilute plates and none at all in the more concentrated ones. It may be that the whole blood itself acts to inhibit the development of the growth. It is well known that whole blood makes every attempt to rid itself of bacteria, and does not lend itself to use as a medium as well as other tissues of the body.

4. Incubation of the plates was continued for ten days. To prevent drying, the plates were inverted as soon as they had set, and were then placed over a basin of water in the incubator. The development of the original culture did not appear in two cases until the eighth day of incubation, and the average time was five days. For this reason, some procedure was necessary to prevent drying of the plates, for under the usual conditions the plates dried on the third or fourth day.

5. Transplantation was made as soon as the earliest colony appeared, for in the original culture, there seemed to be only a low degree of viability. More frequently than otherwise no transplant was obtained after waiting for the culture to develop fully. Up to a certain point these cultures seemed to increase in viability by transplantation, but the majority of our cultures did not survive six or eight transplantations.

6. The character of the growth in the original blood culture was not always typically that of *Streptococcus viridans*. Only three produced green in the original culture, but the remaining 11 did so in the transplants. These original colonies appeared like little black spots that could be seen only in a good light. In addition to the fourteen positive blood cultures herein reported we obtained six additional cultures which we were unable to transplant. These colonies were of the type just described; they retained the Gram stain, and presented on the slide the morphology of the other colonies which were transplanted and identified.

7. Identification of the transplants was done by Dr. Thro. All transplants had the same cultural characters:

Did not break up in bile
Did not peptonize milk
Grew in chains in broth
Produced green in blood
Retained the Gram stain
Were of low grade virulency to rabbits

Blood cultures were taken in 104 cases and this organism was found in 14 cases, and no bacteria but this organism were found in any culture. The organism in question can be classed as *Streptococcus viridans*. Control cultures were made from the blood of other patients and no growth of this organism was obtained.

Complement fixation tests with *Streptococcus viridans* antigens were done in all cases. The technique of complement fixation was based on the work of Schwartz and MacNeil (1911) in their study of complement fixation in gonorrhoeal infections, and on the

work of Swift and Thro (1911) in their study of streptococci by the use of complement fixation. The difficulties of the test lie in the preparation of efficient antigens. The one that has given most satisfactory results in our hands is the unkilled, thoroughly washed, salt ground bacterial emulsion. In our comparative experiments this method gave a greater difference between the fixing power and the anticomplementary dose than the Besredka dried antigen, the heated and killed bacterial emulsion, or the extracted filtered antigen. Swift and Throfound the fixing power of an extract made from dried bacteria highest compared to the anticomplementary power. At the beginning of this work, several antigens (5 to 9) prepared from different strains of *Streptococcus viridans* were used. Hastings (1914) found the necessity for the employment of many antigens to be due to the fact that a group reaction could not be obtained. We also found this necessary when working with an antigen of high anticomplementary action. But when an antigen was prepared as just described a polyvalent antigen of pooled strains all from Arthritis deformans gave satisfactory results on account of the higher fixing power—anticomplementary ratio. This is illustrated by the results of case 25 on the table appended. An autogenous antigen was not found more efficient than this polyvalent antigen excepting in case 6. In this case we obtained no inhibition excepting with an antigen prepared from an autogenous tooth culture. For the past two years our bacterial vaccines have been standardized by their nitrogen content. This has been found much more accurate than the Wright method of counting, Of late it has been found convenient to determine a working dilution of our antigens by this method, and usually the fixing power and the anti-complementary dose could be determined in a dilution containing 0.000028 gram bacterial nitrogen per cubic centimeter.

Joint cultures were attempted in 54 cases and *Streptococcus viridans* was obtained in 4 cases. These cultures were taken during an acute exacerbation, and an attempt was made to obtain fluid from the inflamed periarticular tissues as well as from the joint cavity.

TABLE 1

Determination of anticomplementary and fixing power of different antigens with serum from case 25

SERUM CASE 25	ANTIGEN	A	B	C	D	E	F	G	H	I	J
cc.	cc.										
0	0.05	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0	0.06	0+++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0	0.07	0+++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0	0.08	0+++	0+++	++++	++++	++++	++++	+++0	++++	++++	++++
0	0.09	0 0++	0+++	++++	++++	++++	++++	++++	++++	++++	++++
0	0.10	0 0++	0 0++	0+++	++++	++++	++++	++++	++++	++++	++++
0	0.11	0 0 0 0	0 0 0+	0+++	++++	++++	++++	++++	++++	++++	++++
0	0.12	0 0 0 0	0 0 0 0	0 0++	++++	++++	++++	++++	++++	++++	++++
0	0.13	0 0 0 0	0 0 0 0	0 0 0 0	++++	++++	++++	++++	++++	++++	0+++
0	0.14	0 0 0 0	0 0 0 0	0 0 0 0	++++	++++	++++	++++	++++	++++	0+++
0.02	0.01	0 0 0 0	0+++	0 0++	0+++	0 0 0+	0 0++	0+++	0 0 0 0	0 0 0+	0+++
0.02	0.02	0 0 0 0	0 0++	0+++	0 0 0+	0 0 0 0	0 0 0+	0 0++	0 0 0 0	0 0 0+	0+++
0.02	0.03	0 0 0 0	0 0++	0 0++	0 0 0 0	0 0 0 0	0 0 0 0	0 0++	0 0 0 0	0 0 0+	0+++
0.02	0.04	0 0 0 0	0 0++	0 0 0+	0 0 0 0	0 0 0 0	0 0 0 0	0 0++	0 0 0 0	0 0 0+	0 0++
0.02	0.05	0 0 0 0	0 0++	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0++	0 0 0 0	0 0 0 0	0 0 0+
0.02	0.06	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0+	0 0 0 0	0 0 0 0	0 0 0+
0.02	0.07	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0+	0 0 0 0	0 0 0 0	0 0 0+
0.02	0.08	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0+	0 0 0 0	0 0 0 0	0 0 0

++++ = complete hemolysis.
0+++ = about 75 per cent hemolysis.
0 0++ = about 50 per cent hemolysis.
0 0 0+ = about 25 per cent hemolysis.
0 0 0 0 = complete inhibition.
A = Washed, unkilled, bacterial emulsion of pooled strains.
B = Washed, killed by 60°C. one hour, bacterial emulsion of pooled strains.
C = Besredka extract of pooled strains.
D = Washed, salt ground bacterial emulsion of pooled strains.
E = Washed, salt ground bacterial emulsion of strain 1.
F = Washed, salt ground bacterial emulsion of strain 2.
G = Washed, salt ground bacterial emulsion of strain 3.
H = Washed, salt ground bacterial emulsion of strain 4.
I = Washed, salt ground bacterial emulsion of strain 5.
J = Washed, salt ground bacterial emulsion of autogenous strain.

The feces of all cases was examined by Gram stain, and those that showed streptococci on the slide were cultured. Streptococci were found by the Gram stain in 42 cases, and were isolated and identified as *Streptococcus viridans* in 5 cases. This is an interesting phase of the work and we are continuing work along this line. The technique of making these cultures was as follows: Select a loopful of clear mucus, wash thoroughly in saline, and plant several plates very thinly. Even by this method we had great difficulty in obtaining the five positive cultures on account of the rapid overgrowth of other bacteria found in the stool.

The technique of culture of the various foci is as follows:

Teeth. When a sinus or pyorrhoea was present a culture was taken directly from the pus. This pus was usually found to contain two or more types of bacteria. When a tooth was withdrawn a culture was taken from the root and the socket, and frequently *Streptococcus viridans* was found in pure culture.

Tonsil. After gargling with sterile saline a loop was inserted as deeply as possible into a crypt of the tonsil using a pillar retractor when necessary for a clear view. If the tonsils were removed a culture was made from the deeper portions through an incision of the tonsillar capsule.

Ethmoid and sphenoid cultures were taken from the discharges from these sinuses after cleansing the nasal cavity with sterile salt solution. The material to be planted was taken as nearly as possible from the opening of these sinuses. In cases 3 and 7 the cultures were taken directly from the sinuses during an operation by E. Ross Faulkner. The other nasal sinuses were cultured in a similar manner.

Prostate. After urinating, the prostate was massaged and the culture made directly from the discharge.

Pyelitis. The sediment from a freshly catheterized urine was immediately planted on North's medium.

Salpingitis. The one case was cultured at the time of operation.

From a study of the table herein appended giving a summary of the 104 cases it is found that

1. In blood cultures *Streptococcus viridans* was found in 14 cases out of 104 cases.

TABLE 2

Review of cases of arthritis

CASE NUMBER	SEX	AGE	STREPTOCOCCUS VIRIDANS COMPLEMENT FIXATION	STREPTOCOCCUS VIRIDANS BLOOD-CULTURE	STREPTOCOCCUS VIRIDANS JOINT-CULTURE	STREPTOCOCCUS VIRIDANS FECES-CULTURE	STREPTOCOCCUS FECES GRAM-STAIN	PAST HISTORY OF CHOREA-ACUTE RHEUMATIC FEVER CHRONIC ENDOCARDITIS	STREPTOCOCCUS VIRIDANS FOCUS TEETH	STREPTOCOCCUS VIRIDANS FOCUS TONSIL	OTHER STREPTOCOCCUS VIRIDANS FOCI
1	M.	38	+	+		0	+	Chronic endocarditis	+	+	
2	M.	41	+	+		+	+		0	+	
3	M.	40	+	+	+	0	+	Acute rheumatic fever	+	+	Ethmoids, sphenoids
4	F.	44	0	+	0	0	+	Chronic endocarditis	+	+	
5	F.	49	+	+		0	+		+	+	
6	F.	44	+	+	0	0	+		+	0	
7	M.	50	+	+		0	+		+	0	Ethmoids, maxillary
8	F.	52	+	+			0		0	+	
9	F.	48	+	+			0		+	0	
10	M.	49	+	+	0	+	+		+	+	
11	F.	46	0	+	+	+	+		0	+	
12	F.	58	+	+	0		0		+	+	
13	M.	39	+	+	0		0	Chronic endocarditis	0	0	Prostate
14	F.	36	+	+	0	0	+		0	+	
15	M.	40	0	0	0		0	Chronic endocarditis, acute rheumatic fever	0	0	
16	M.	39	0	0	−	+	+		+	0	
17	F.	46	0	0		0	+	Acute rheumatic fever	+	0	
18	F.	35	0	0	0	0	+		0	+	
19	M.	47	+	0			0		+	+	
20	M.	39	+	0	0		0	Acute rheumatic fever	0	0	
21	M.	51	0	0		0	+		+	0	
22	F.	52	+	0		0	+		0	0	
23	F.	49	+	0			0		0	+	
24	F.	42	+	0			0	Chronic endocarditis	0	0	
25	F.	44	+	0			0		+	+	

TABLE 2—*Continued*

CASE NUMBER	SEX	AGE	STREPTOCOCCUS VIRIDANS COMPLEMENT FIXATION	STREPTOCOCCUS VIRIDANS BLOOD-CULTURE	STREPTOCOCCUS VIRIDANS JOINT-CULTURE	STREPTOCOCCUS VIRIDANS FECES-CULTURE	STREPTOCOCCUS FECES GRAM-STAIN	PAST HISTORY OF CHOREA-ACUTE RHEUMATIC FEVER CHRONIC ENDOCARDITIS	STREPTOCOCCUS VIRIDANS FOCUS TEETH	STREPTOCOCCUS VIRIDANS FOCUS TONSIL	OTHER STREPTOCOCCUS VIRIDANS FOCI.
26	M.	49	+	0		0	+		0	0	
27	M.	47	0	0	0	0	+		+	0	Ethmoids
28	M.	60	+	0	0	0	+		+	0	
29	M.	62	+	0	0	0	+		0	0	
30	M.	59	0	0	0	0	+		+	+	
31	F.	48	+	0		0	+		0	+	
32	F.	38	+	0		0	+		0	+	
33	M.	47	+	0	0		0		0	0	
34	M.	36	0	0	0	0	+		+	0	
35	F.	29	+	0	0		0		0	0	
36	M.	52	+	0	0		0		0	0	
37	F.	54	0	0	0	0	+		0	0	
38	M.	30	+	0	0	0	+		0	0	
39	M.	38	+	0	0		0		0	0	Ethmoids
40	M.	44	0	0	0		0	Acute rheumatic fever	0	0	
41	M.	36	+	0	0		0	Acute rheumatic fever	+		
42	M.	38	+	0	+		0		+	0	
43	M.	61	0	0			0	Chronic endocarditis	+	+	
44	F.	57	+	0			0		+	0	
45	F.	55	+	0	0		0		+	+	
46	F.	53	0	0	0	0	+		+	0	
47	F.	46	+	0		0	+		+	0	
48	F.	48	+	0		0	+		0	0	
49	F.	57	+	0			0		+	+	
50	M.	46	+	0			0	Acute rheumatic fever	0	0	
51	M.	51	0	0			0		0	0	
52	F.	42	+	0	0	0	+		+	+	
53	F.	51	+	0			0		+	0	
54	M.	52	+	0	0		0		+	+	
55	M.	41	0	0			0	Chronic endocarditis	+	+	
56	M.	43	+	0	0		0		0	0	

TABLE 2—*Continued*

CASE NUMBER	SEX	AGE	STREPTOCOCCUS VIRIDANS COMPLEMENT FIXATION	STREPTOCOCCUS VIRIDANS BLOOD-CULTURE	STREPTOCOCCUS VIRIDANS JOINT-CULTURE	STREPTOCOCCUS VIRIDANS FECES-CULTURE	STREPTOCOCCUS FECES GRAM-STAIN	PAST HISTORY OF CHOREA-ACUTE RHEUMATIC FEVER CHRONIC ENDOCARDITIS	STREPTOCOCCUS VIRIDANS FOCUS TEETH	STREPTOCOCCUS VIRIDANS FOCUS TONSIL	OTHER STREPTOCOCCUS VIRIDANS FOCI
57	M.	45	+	0			0	Acute rheumatic fever	0	+	
58	M.	52	+	0	0		0	Chronic endocarditis	+	0	
59	M.	53	+	0	0	0	+		0	+	
60	M.	45	0	0	0		0		0	+	
61	M.	47	+	0		0	+		0	0	
62	M.	51	+	0		0	+		+	0	
63	F.	48	0	0	0	0	+	Acute rheumatic fever	+	0	
64	F.	39	+	0		0	+		0	0	
65	F.	64	0	0			0		+	0	
66	F.	48	0	0	0		0		0	+	
67	F.	62	0	0			0		0	0	
68	F.	11	+	0			0	Chorea	+	0	Ethmoids, sphenoids
69	M.	19	+	0			0		0	0	
70	F.	28	+	0			0		0	0	
71	M.	42	0	0	0		0		0	+	
72	F.	41	+	0		+	+		+	0	
73	M.	15	+	0			0		+	0	
74	F.	35					0		+	0	
75	F.	36	0	0	0	0	+	Chronic endocarditis	+	+	
76	M.	34	+	0	0		0	Acute rheumatic fever	0	0	
77	M.	48	0	0			0		+	0	
78	M.	51	+	0			0		0	0	
79	M.	39	+	0			0		0	0	
80	F.	33	+	0	0	0	+	Chronic endocarditis	+	+	
81	F.	46	+	0	+		0		+	+	
82	F.	44	+	0	0		0	Acute rheumatic fever	+	+	Maxillary
83	M.	41	0	0			0		+	0	
84	F.	17	0	0			0	Chorea	0	0	

TABLE 2—*Concluded*

CASE NUMBER	SEX	AGE	STREPTOCOCCUS VIRIDANS COMPLEMENT FIXATION	STREPTOCOCCUS VIRIDANS BLOOD-CULTURE	STREPTOCOCCUS VIRIDANS JOINT-CULTURE	STREPTOCOCCUS VIRIDANS FECES-CULTURE	STREPTOCOCCUS FECES GRAM-STAIN	PAST HISTORY OF CHOREA-ACUTE RHEUMATIC FEVER CHRONIC ENDOCARDITIS	STREPTOCOCCUS VIRIDANS FOCUS TEETH	STREPTOCOCCUS VIRIDANS FOCUS TONSIL	OTHER STREPTOCOCCUS VIRIDANS FOCI
85	F.	28	0	0		0	+		0	0	
86	M.	39	0	0	0		0		0	0	
87	M	44	0	0	0		0		0	0	
88	F.	52	+	0		0	+		0	+	
89	F.	52	+	0		0	+		+	0	
90	F.	68	+	0			0		+	0	
91	F.	38	0	0	0		0		0	+	
92	F.	37	0	0	0		0		0	0	Kidney-pelvis
93	F.	39	+	0	0		0	Chronic endocarditis	+	+	
94	M.	44	0	0	0		0		+	+	
95	M.	46	+	0	0		0		+	0	
96	F.	37	+	0	0	0	+		0	0	
97	M.	41	+	0	0	0	+		0	+	
98	F.	36	0	0			0		0	+	
99	F.	42	+	0	0		0		0	0	
101	F.	50	+	0	0		0		0	+	
102	F.	36	+	0	0		0		0	+	
103	F.	48	0	0			0		0	0	
104	F.	39	0	0			0	Acute rheumatic fever	0	0	
100	M.	46	+	0	0		0		+	0	Prostate

In all cases Wassermann and gonococcus fixation tests were negative.

2. Chronic endocarditis was found in 11 cases.
3. A history of acute rheumatic fever was obtained in 12 cases.
4. A history of chorea in 2 cases.
5. Foci of *Streptococcus viridans* infection were found:

	Cases
Teeth	50
Tonsils	40
Ethmoid	5
Frontal	0
Sphenoid	2
Antrum	4

	Cases
Prostate	2
Pyelitis	1
Salpingitis	1

6. Complement fixation with *Streptococcus viridans* antigen was found positive in 68 cases.

7. Joint fluid cultures demonstrated *Streptococcus viridans* in 4 out of 54 cases.

8. No foci of *Streptococcus viridans* infection were found in 20 cases, and of these 20 negative cases 11 gave positive complement fixation tests. In addition to these 20 cases, there were 9 cases in which a streptococcus was seen in the Gram stain of the stool but could not be obtained in culture for identification, and of these, 7 gave positive complement fixation tests with *Streptococcus viridans* antigen.

TABLE 3

Review of cases of chorea

CASE NUMBER	SEX	AGE	WASSERMANN	GONOCOCCUS FIXATION	STREPTOCOCCUS VIRIDANS FIXATION	STREPTOCOCCUS VIRIDANS BLOOD CULTURE	STREPTOCOCCUS VIRIDANS FECES-CULTURE	STREPTOCOCCUS FECES GRAM-STAIN	ENDOCARDITIS	HISTORY ACUTE RHEUMATIC FEVER	PRESENT INFLAMMATION JOINTS	STREPTOCOCCUS VIRIDANS FOCUS TEETH	STREPTOCOCCUS VIRIDANS FOCUS TONSIL	STREPTOCOCCUS VIRIDANS FOCUS NOSE	GONOCOCCUS FOCUS VAGINA	DURATION OF CHOREA
1	F.	13	0	0	+	0	0	+	+	0	0	+	+	0		11 days
2	F.	9	+	0	+	0	0	+	+	0	0	0	+	0		5 weeks
3	F.	14	0	0	+	0	+	+	0	0	+	+	+	0		7 days
4	F.	15	0	0	+	0	0	+	0	+	0	+	+	+		2 weeks
5	F.	11	+	0	0	0	0	0	+	0	+	0	0	0		2 weeks
6	F.	11	0	+	0	0	0	0	0	0	0	0	0	0	+	9 days
7	F.	18	0	0	+	+	+	+	0	0	0	+	+	+		4 weeks
8	M.	9	0	0	+	0	0	0	+	0	0	0	0	0		8 weeks
9	M.	8	0	0	+	+	0	0	+	0	+	0	0	0		10 days
10	M.	14	0	0	+	+	0	+	+	0	0	+	0	0		7 weeks
11	F.	14	0	0	+	0	0	+	+	0	0	+	+	+		4 weeks
12	F.	10	0	0	+	+	+	+	+	0	+	+	0	0		11 days
13	F.	10	0	0	+	+	0	+	+	0	0	0	+	+		15 days
14	F.	13	0	0	+	0	0	0	0	0	0	0	0	+		5 days
15	M.	9	0	0	+	0	0	0	+	0	0	+	+	0		18 days
16	F.	19	0	0	0	0	0	0	0	+	0	0	+	0		11 weeks

II. BACTERIOLOGIC STUDIES IN CHOREA

In January 10, 1913, I reported two cases of chorea in which *Streptococcus viridans* was found in the blood. Since that time I have studied 16 cases in addition. The technique of cultures and complement fixation was the same as was used in the bacteriologic studies in chronic arthritis just reported. In cases 2 and 5 the Wassermann reaction was positive In case 2 there were no other signs of lues, and on account of the absence of both parents, hereditary lues could not be established. Case 5 had an interstitial keratitis, and the mother gave a positive history of lues contracted from the father. Case 6 gave a positive gonococcus fixation test, and was found to have a history of eight months leucorrhoea in which gonococci were found. In this case we could find no focus of *Streptococcus viridans* infection, and the complement fixation was negative with *Streptococcus viridans* antigen. Altogether in 4 cases no focus of *Streptococcus viridans* infection was found. The complement fixation with *Streptococcus viridans* antigen was positive in 13 cases, and negative in 3. The blood cultures showed *Streptococcus viridans* positive in 5, and negative in 11 cases. The feces cultures showed *Streptococcus viridans* in 3 cases, but Gram stain streptococci were found in 9 cases. Other foci of *Streptococcus viridans* infection were found in

	Cases
Tonsils	9
Teeth	8
Nose	5

All cultures were isolated and identified in the manner just described in the bacteriologic studies of chronic arthritis.

REFERENCES

BEATTIS AND YATES 1912–1913 J. Path. & Bact., **17**, 538–551.
BESREDKA 1904 Ann. de l'Inst. Pasteur, **18**, 363.
COLE, R. I. 1914 J. Infect. Dis., **1**, 714–737.
DAVIS, D. J. 1913 J. A. M. A., **61**, 724–727.
FABER, H. K. 1915 J. Exp. Med., **22**, 615–638.
HASTINGS, T. W. 1914 J. Exp. Med., **20**, no. 1.
MOON AND EDWARDS 1917 J. Infect. Dis. Chi., **21**, 154–161.
NORTH, C. E. 1909 J. Med. Research, **20**, 359.
POYNTON AND PAINE 1913 Complete works. London, p. 109.
ROSENOW, E. C. 1914 J. Infect. Dis., **14**, 61; J. A. M. A., **63**, 905.
SCHWARTZ AND MACNEIL 1911 A. J. Med. Sci., **141**, 693.
SWIFT AND KINSELLA 1917 Arch. Int. Med., **19**, 381.
SWIFT AND THRO 1911 Arch. Int. Med., **7**, 24–27.